.5
504
4
v.9
6

JAPANESE HEART JOURNAL

THE UNIVERSITY OF MICHIGAN
FEB 17 1969
MEDICAL LIBRARY

Vol. 9
No. 6
November, 1968

Published Bimonthly by

Japanese Heart Journal Association

Editorial Office :
The Second Department of Internal Medicine,
Faculty of Medicine, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo, Japan

Jap. Heart J.

For the treatment of
Congestive Heart Failure
and Arrhythmia

CARDIOTONIC AND DIURETIC PREPARATION

DIGITOXIN tab.

"SHIONOGI"

DIGITOXIN Tablet "Shionogi" is essentially a purified crystalline cardiotonic glucoside extracted from digitalis purpurea cultivated at Shionogi's farm.
The purity and potency of the preparation conforms to the U.S.P. specification.

CHARACTERISTICS:

1. Digitoxin is 1,000 times more effective than the powdered leaf digitalis, in weight basis.
2. Digitoxin has the advantage of greater accuracy of dosage in comparison with the powdered leaf digitalis.
3. Digitoxin is almost completely absorbed after oral administration.

SUPPLIED:

Available as 0.1mg. Scored tablet. Bottles of 100.

SHIONOGI & CO., LTD.

No. 12, 3-Chome, Doshomachi, Higashi-ku,
Osaka, Japan.

Synergistic Pharmacological Effect From A Combination of 38 Vitamins!

Benfotiamine
Plus Vitamin B_6
and B_{12}

A Highly Neurotropic Agent

VITAMEDIN

SANKYO CO., LTD.

Available in a variety of dosage forms and bulk quantities

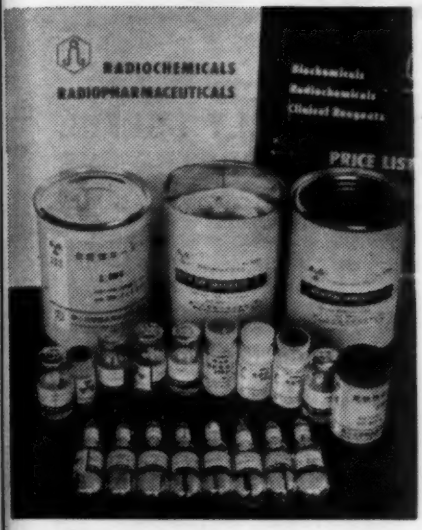
PHARMACEUTICAL SPECIALITIES
PHARMACEUTICAL CHEMICALS
CHEMICALS FOR FOOD INDUSTRY
VETERINARY MEDICINES

MANUFACTURING CHEMISTS

TANABE SEIYAKU CO., LTD.

21 DOSHO-MACHI 3-CHOME, HIGASHI-KU, OSAKA, JAPAN

RADIOPHARMACEUTICALS



I^{131}-Labeled Compounds

I^{131}-Human Serum Albumin Injection

I^{131}-o-Iodohippurate Injection

I^{131}-Rose Bengal Injection

I^{131}-Triolein, Capsule

Sodium I^{131}-Tablet, Capsule, Solution

I^{131}-Macro Aggregated Albumin

I^{131}-Aggregated Albumin

etc.

I^{125}-Labeled Compounds

RADIOCHEMICALS

C^{14}-Labeled Compounds

H^3-Labeled Compounds

Other Labeled Compounds

We successfully started manufacture of isotope labeled compound in 1955 and have established the foremost position in producing labeled compound of various radioisotopes and radiopharmaceuticals in Japan. The excellent laboratory staff and technique of us will fulfil your need.

Each lot of our products is subjected to dilution analysis, paper chromatography and other tests, to establish radiochemical purity. Chemicals and pharmaceuticals are always "packed" in the form most compatible with chemical and radiation stability. We ask you to give us your order and put radiochemicals and radiopharmaceuticals from the DAIICHI PURE CHEMICALS CO., LTD. to test. Pamphlet and literature will be sent on request.

Rider Brand

DAIICHI PURE CHEMICALS CO., LTD.

No. 7, 3-chome, Honcho, Nihonbashi, Chuo-ku, Tokyo, Japan

Renese®
POLYTHIAZIDE

1 mg. 2 mg. 4 mg.

A MORE CLINICALLY USEFUL DIURETIC/ANTIHYPERTENSIVE

active antihypertensive	marked micturition
broad benefit	notable natruresis
clinically confirmed	orally optimal
convenient control	peak potency
dosage dexterity	prolonged performance
dependable diuresis	reliable response
enhanced effectiveness	significant saluresis
foremost flexibility	tested toleration
increased individualization	unsurpassed utility
long lasting	valuable versatility

"active antihypertensive" —RENESE is a highly effective antihypertensive agent when used alone or concomitantly with other agents such as rauwolfia or blocking agents. Excellent-to-good clinical response has been reported in 145 out of 180 patients with hypertension alone and in 109 out of 128 patients with hypertension and associated congestive heart failure. Some of these patients had been refractory to previous therapy.

Pfizer *Science for the world's well-being®*

PFIZER TAITO COMPANY, LTD.
YANAGIYA BUILDING
NO. 2, TORI 2-CHOME, NIHONBASHI
CHUO-KU, TOKYO, JAPAN

Editor-in-Chief

Hideo UEDA, M. D.

Professor of Internal Medicine, University of Tokyo, Tokyo

Advisory Board

Magojiro MAEKAWA, M.D.
Emeritus Professor of Internal Medicine,
Kyoto University, Kyoto

Shigeo OKINAKA, M.D.
Emeritus Professor of Internal Medicine
University of Tokyo, Tokyo

Editorial Board

Toyozo AIZAWA, M.D.
Professor of Internal Medicine,
Keio University, Tokyo

Shingo AOYAMA, M.D.
Professor of Internal Medicine,
Nagoya University, Nagoya

Kyo HARA, M.D.
Professor of Internal Medicine,
Osaka Medical College, Osaka

Susumu HIBINO, M.D.
Professor of Internal Medicine,
Nagoya University, Nagoya

Koichi ISHIKAWA, M.D.
Professor of Surgery,
University of Tokyo, Tokyo

Seiji KIMOTO, M.D.
Professor of Surgery,
University of Tokyo, Tokyo

Eiichi KIMURA, M.D.
Professor of Internal Medicine,
Nippon Medical School, Tokyo

Noboru KIMURA, M.D.
Professor of Internal Medicine,
Kurume University, Kurume

Tachio KOBAYASHI, M.D.
Professor of Internal Medicine,
University of Tokyo, Tokyo

Kojiro MATSUDA, M.D.
Professor of Physiology,
University of Tokyo, Tokyo

Shigeru MATSUOKA, M.D.
Professor of Pathology,
Nagasaki University, Nagasaki

Mototaka MURAKAMI, M.D.
Professor of Internal Medicine,
Kanazawa University, Kanazawa

Takashi NAKAMURA, M.D.
Professor of Internal Medicine,
Tohoku University, Sendai

Kiku NAKAO, M.D.
Professor of Internal Medicine,
University of Tokyo, Tokyo

Masaya NISHIMURA, M.D.
Professor of Surgery,
Kyushu University, Fukuoka

Kenzo OSHIMA, M.D.
Professor of Internal Medicine,
Nihon University, Tokyo

Yoshio OSHIMA, M.D.
Professor of Physical Therapy and Medicine,
University of Tokyo, Tokyo

Soroku SAITOH, M.D.
Professor of Internal Medicine,
Chiba University, Chiba

Shigeru SAKAKIBARA, M.D.
Professor of Surgery,
Tokyo Women's Medical College, Tokyo

Toyomi SANO, M.D.
Professor of Clinical Physiology and Internal Medicine,
Tokyo Medical and Dental University, Tokyo

Takio SHIMAMOTO, M.D.
Professor of Internal Medicine,
Tokyo Medical and Dental University, Tokyo

Masao TAKAYASU, M.D.
Professor of Internal Medicine,
Kyoto University, Kyoto

Fumio TAKENAKA, M.D.
Professor of Pharmacology,
Kumamoto University, Kumamoto

Masao TAMAKI, M.D.
Professor of Radiology,
Osaka City University, Osaka

Tatsuya TOMOMATSU, M.D.
Professor of Internal Medicine,
Kobe Medical College, Kobe

Tatsuo TORIKAI, M.D.
Professor of Internal Medicine,
Tohoku University, Sendai

Kazuo YAMADA, M.D.
Professor, Division of Circulation,
Institute of Environmental Medicine,
Nagoya University, Nagoya

Yawara YOSHITOSHI, M.D.
Professor of Internal Medicine,
University of Tokyo, Tokyo

Technical Editors

Jugoro TAKEUCHI, M.D.
Professor of Internal Medicine,
Kanazawa University, Kanazawa

Satoru MURAO, M.D.
Associate Professor of Internal Medicine,
University of Tokyo, Tokyo

Iwao ITO, M.D.
Assistant Professor of Internal Medicine,
University of Tokyo, Tokyo

Hisakazu YASUDA, M.D.
Instructor of Internal Medicine
University of Tokyo, Tokyo

Information for Authors

Original Communications:

Manuscripts for publication, letters, and all other editorial communications should be sent to the following address:

Hideo Ueda, M.D., Editor-in-Chief
The Second Department of Internal Medicine
Faculty of Medicine, University of Tokyo
Hongo, Bunkyo-ku, Tokyo, Japan

A paper for publication may be submitted from any country of the world but its acceptability depends upon editorial decision.

Manuscripts:

Manuscripts should be typewritten on good quality paper, one side of the page only, with double or triple spacing and liberal margins. Pages should be numbered.

Papers for publication in this journal may be submitted as original articles, as special articles, as case reports, or as editorials.

The first page should contain: title of paper; names of authors with academic degrees; department and institution in which the work was done, including city and state; if authors wish, the sources of the grant support; a running head not to exceed 50 letters including spaces between words; complete address for mailing of proofs.

The second page of original articles, special articles and case reports should contain a summary and up to 10 indexing words or phrases not used in the title

The introduction to a paper should be a brief statement of the specific problem and its relation to the somewhat larger area of the field with which the subject is concerned.

Original articles should, as a general rule, be organized under the following headings: methods (or materials and methods); results; discussion.

References to literature cited should be numbered serially, in parentheses, in the text and listed in the same order on a separate sheet at the end of the manuscript, giving authors' names and initials, and the name, volume number, page number and year of publication of the journal, in that order. Book references should be in the following order: author; title (with number of edition); publisher; city of publisher; page and year.

Illustrations and Tables:

Illustrations (unmounted photographs) should be identified on the reverse with figure number and author name(s); when necessary the top should be clearly marked. Legends for illustration should be typed on separate sheets, double spaced. Color plates will not be accepted.

Each table should be typed on a separate sheet and have a brief heading; explanatory matter should be in footnotes, not as part of the title.

Approximate position of figures and tables should be indicated in the margin of the manuscript.

Expense of Publication:

Publication of a paper is allowed without charge unless it exceeds **8 pages** including figures and tables. Case reports should not exceed **5 pages.** Additional 5 pages may be allowed at the expense (U.S. $14.00 for one page) of the author or his supporting funds. U.S. $28.00 per one page will be charged for further excess.

Reprints:

Each author receives with his galley proofs a reprint order form which must be completed and returned to the editorial office with the proofs. Twenty free of charge reprints will be given to the author or divided among the authors.

Editorial

Afferent Impulses in the Renal Nerves

Hideo Ueda, M. D. *and* Yasumi Uchida, M. D.

IT has not been settled whether there are receptors having baroreceptive functions in the kidney. Page and McCubbin studied the systemic arterial pressure responses to nervous and chemical stimulation of the kidney and found no baroreceptors or chemoreceptors in the kidney.[9] Heymans observed no reflex in the perfused kidneys of spinal dogs.[4] On the other hand, Irisawa found a fall in systemic arterial pressure during elevation of the pressure in a blind sack preparation of the renal artery, and suggested the existence of baroreceptors in the wall of the renal artery.[5] Likewise, Ueda and his coworkers observed reflex hypotension during elevation of the perfusion pressure in the kidney of dogs, and suggested the existence of a depressor reflex originating from the kidney.[14]

The centripetal impulses in the renal nerves were recorded by several workers.[2),7),8),10),13] Äström and Crafood showed two types of the impulses in rats; the ones of rapidly adapting and of slowly adapting. However, they observed no impulses discharging spontaneously.[2] We studied the afferent impulses in dogs and found two types which were different in the mode of excitation in response to mechanical stimuli; the impulses of low voltages, spontaneously discharging and of slowly adapting (type A), and the ones of higher voltages and threshold, not spontaneously discharging, and of rapidly adapting (type B). Two discharge patterns were observed in type A impulses; the ones which were discharging irregularly with no relations to renal arterial, venous or intrarenal pressure waves, and the ones which were discharging regularly at the ascents of the intrarenal pressure waves, but not at the ascents of the renal arterial pressure waves. The number of the both impulses changed with a rise or fall of mean intrarenal pressure.[16]

The afferent impulses in the renal nerves were increased by compression of the surface of the kidney,[2),7),11),15] by occlusion of the renal vein,[10),15] by elevation of the perfusion pressure in the renal artery,[8] and by elevation of the intrapelvic pressure.[15] The impulses of the both types appeared or increased during these manēuvers in our experiments.[16]

* From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo.

As to the direct stimuli activating the renal receptors, an increase in renal arterial pressure[1] and an increase in renal venous pressure were suggested.[10] Åström concluded that the slowly adapting spikes were activated by increased intrarenal tension, while the rapidly adapting spikes by increased venous pressure.[2] In our experiments in which intrarenal pressure was changed toward different directions with renal arterial or venous pressure, the afferent impulses of both types increased or decreased respectively with a rise or fall in intrarenal pressure, but not associated directly with changes in renal arterial pressure or in renal venous pressure.[16]

The type A impulses increased momentarily at the initiation of a fall in intrarenal pressure and then vanished or decreased following the intravenous injection of vasopressor agents such as norepinephrine, epinephrine, methoxamine or angiotensin II. They increased markedly with a return or overshoot of the intrarenal pressure. The type B impulses appeared momentarily at descending or ascending limbs of intrarenal pressure.[16]

The impulses of both types were recorded even after the renal capsule was resected or after the intrapelvic injection of procaine. However, they disappeared after the injection of procaine into the renal artery.[15]

The impulses recorded appeared to come from receptors locating in the interstitial or fatty tissues in the kidney, but not from receptors in the wall of the renal artery. Fujiwara and others found the nerve endings which they thought to join the medullated fibers in the adventitia of the spiral arteries and their surrounding interstitial tissues or fatty tissues.[1),3),6),11),12]

The efferent renal nerve activity vanished or decreased and was followed by a fall in systemic arterial pressure during compression of the kidney or occlusion of the renal vein.[15] The efferent impulses of a renal nerve was inhibited by electrical stimulation of the cut central end of another renal nerve.[8),15] The systemic arterial pressure decreased as much as 30 mm.Hg during the stimulation of the cut central end of the renal nerve, suggesting that the renal receptors participated in the changes of sympathetic nerve activity and systemic blood pressure.[15] However, it is obscure whether the renal receptors be participating in the regulation of systemic arterial pressure or of renal circulation in physiological conditions.

References

1. Ábráhám, A.: Akadémiai Kiadó Budapest, 1962.
2. Åström, A. and Crafood, J.: Acta Physiol. Scand. **70**: 10, 1967.
3. Fujiwara, S.: J. Jap. Nephrol. **10**: 301, 1968.
4. Heymans, C., Bouckaert, J. J., and Wierzuckewski, M.: Arch. int. Pharmacodyn. **55**: 233, 1937.

5. Irisawa, T.: J. Jap. Soc. Int. Med. **48**: 1262, 1959.
6. Knoche, H.: Z. Zellforsch. **36**: 448, 1951.
7. Niijima, A.: J. Jap. Soc. Physiol. **21**: 477, 1964.
8. Niijima, A.: J. Jap. Soc. Physiol. **27**: 72, 1965.
9. Page, I. H. and McCubbin, J. W.: Am. J. Physiol. **174**: 411, 1953.
10. Pines, I. L.: Fiziol. Zn. USSR, Sechonov. **45**: 1339, 1959.
11. Takeuchi, J.: J. Jap. Soc. Nephrol. **8**: 1, 1963.
12. Takeuchi, J. and Mitsumura, Y.: Saishinigaku **19**: 2853, 1963.
13. Tower, S. S.: J. Physiol. **21**: 477, 1964.
14. Ueda, H., et al.: Jap. Heart J. **5**: 254, 1964.
15. Ueda, H., Uchida, Y., and Kamisaka, K.: Jap. Heart J. **8**: 594, 1967.
16. Ueda, H., Uchida, Y., and Kamisaka, K.: 11th Cogress Nephrol. abst. 213, 1968.

Parenteral Fluid Therapy Following Cardiac Surgery in Childhood

Yoshiaki Tsuchida, M.D., Toshio Nakajo, M.D., Masao Hanawa, M.D., Shigenori Sawaguchi, M.D., Masanobu Ishida, M.D.,* *and* Masahiro Saigusa, M.D.**

Summary

Water and electrolyte balance studies were carried out for 48 hours after operations in small children, who underwent cardiac surgery with or without extracorporeal circulation.

Insensible water loss, obligatory urine water and minimum requirement of water were determined. Serum osmolarity and body weight changes in relation to water intake were examined. An adequate dose of water was concluded to be 1,100 ml./M.²/day to 1,400 ml./M.²/day in the first postoperative day and 1,000 ml./M.²/day to 1,400 ml./M.²/day in the second postoperative day.

Serum Na, K and Cl concentration values were within or close to normal range throughout these studies. Interrelations between intake and gain-or-loss of electrolytes (Na, K and Cl) were examined. It was found that sodium and chloride intake up to 40–50 mEq./M.²/day are advisable.

Additional Indexing Words :
Water Electrolyte Balance study Insensible water loss Maintenance dose Extracorporeal circulation Hemodilution Pulmonary edema

THE purpose of this investigation was to determine suitable parenteral administration of water and electrolytes following cardiac surgery. The study included cases with and without extracorporeal circulation in early childhood.

Overhydration should be avoided after cardiac operation. However, in small children too severe limitation of parenteral fluids will result in metabolic disturbances from dehydration. Because of this, administration of some excess water is advisable, if we can do so safely. So, the prime purpose of this investigation centered upon the measurement not only of minimum require-

From the Second Department of Surgery and the Department of Thoracic Surgery, Faculty of Medicine, University of Tokyo, Tokyo.

* Associate Professor, Department of Surgery

** Professor, Department of Thoracic Surgery

Received for publication July 6, 1968.

ments,[1] but also of the maximum dose of water, which can be safely given.

Administration of sodium or potassium to post-cardiac-surgery patients has been recommended by some authors,[2)–4)] but advised against by others.[1] But no balance study has been performed to determine the daily optimal dose of electrolytes after cardiac surgery.

Materials and Methods

The subjects of this investigation were 20 children, 9 months to 9 years of age, who weighed 5.6 Kg. to 18.5 Kg. and whose body surface area ranged between 0.31 $M.^2$ and 0.83 $M.^2$ Extracorporeal circulation was used in 11 children, and the 9 underwent cardiovascular operations without the pump-oxygenator.

In cases with extracorporeal circulation, a moderate degree of hemodilution was obtained with Ringer's solution. Metabolic acidosis was corrected by 7 per cent sodium bicarbonate solution. Through extracorporeal circulation, 98% oxygen —2% carbon dioxide gas was used in oxygenation and the patients were cooled down to 26°C–32°C esophageal temperature.

All balance studies were carried out in the Thoracic Surgery Department of the Tokyo University Hospital between October, 1964 and September, 1966, during which time no remarkable alternation was made in techniques of the perfusion and the operation.

Each patient was studied for 48 hours from the end of the operation and attended at all times during the study by one of the authors. Throughout the study, each patient was kept in an oxygen tent with 70 to 85 per cent humidity and 18°C to 22°C temperature.

Each patient was weighed before and at the end of operation and 24 and 48 hours after the end of operation. Appropriate deductions were made for urine in the bladder, thoracic catheters, bandages and clamps used to occlude the catheters during weighing. Both in the operating room and the recovery ward, body weights were determined on the same scale, suitable for children under 20 Kg. of weight.

Blood was drawn from each patient before, during and at the end of operation and 2, 6, 24 and 48 hours after the end of operation. Each blood sample was used to determine hematocrit, plasma protein, serum Na, K, Cl concentration values and serum osmolarity.

Urine was collected by spontaneous urination or catheter sampling. Catheter urine was obtained every 3 or 4 hours in cases of female children. The volume and specific gravity of urine were measured and thereafter urinary osmolarity and Na, K and Cl concentrations were determined.

Stool did not occur during the study of any patient in this series. Small amounts of vomitus were estimated and, when larger, volumes were measured and Na, K and Cl concentrations were determined.

Drainage from mediastinal spaces, thoracic and pericardial cavities was collected in glass cylinders calibrated in 5 ml. increments and regarded as blood loss of the same constitution as the circulating blood. Throughout the study, blood from tube-drainage and that drawn for examination was replaced volumetrically by blood preserved in ACD solution, which was calculated as 4 parts of blood and 1

Table I. Multiple Electrolyte Solution and Standard Maintenance Dose of Water and Electrolyte

	Multiple Electrolyte Solution	
	Solution A	Solution B
Sodium	30 mEq./L.	35 mEq./L.
Potassium	0	20 mEq./L.
Chloride	20 mEq./L.	35 mEq./L.
Lactate	10 mEq./L.	20 mEq./L.
Glucose	4.3 W/V%	4.3 W/V%

	Standard Maintenance Dose	
	First Postoperative Day	Second Postoperative Day
Water	1,200 ml./M.²/day	1,500 ml./M./day
Sodium	36 mEq./M.²/day	52.5 mEq./M.²/day
Potassium	0	30 mEq./M.²/day
Chloride	24 mEq./M.²/day	52.5 mEq./M.²/day

part of ACD solution.

Surface area was calculated from the equation of Du Bois and Du Bois.[5] All data in this study are expressed in terms of 1 M.² body surface per 24 hours.

Multiple electrolyte solution was given by an intravenous catheter at approximately the same rate through 24 hours. Solution A (Table I) was given on the first postoperative day at a standard maintenance rate of 1,200 ml./M.²/day and Solution B was given on the second postoperative day at a standard maintenance rate of 1,500 ml./M.²/day. Peroral intake of water and electrolytes was not allowed in any cases on the first postoperative day and in a few patients small amounts of Solution B were given orally on the second postoperative day. The volume of administered fluid was measured by the scale on the side of the bottle, the accuracy of which was checked by a glass cylinder afterwards. The volume of each injection such as cardiotonics, antibiotics, hemostatics and analgesics was recorded and Na, K and Cl concentrations were determined. Electrolytes in these injections were of considerable amounts.

Calculations

All water given parenterally (Solution A, Solution B, injections, ACD solution and plasma component of ACD preserved blood) and given orally (Solution B) are calculated as total intake of water. All sodium in solutions above is calculated as total intake of sodium.

Water or sodium in vomitus and plasma component of blood loss are abnormal loss of water or sodium. Maintenance dose of water or sodium, which is more important than total intake in analysing water and electrolyte metabolism, was calculated as the following.

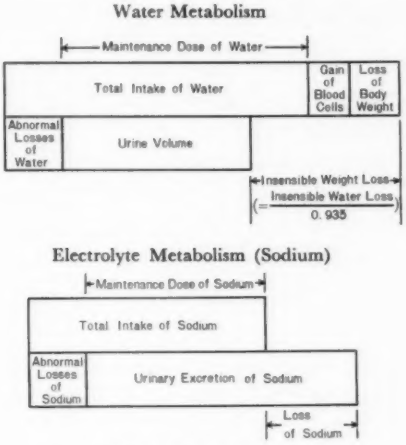


Fig. 1. Calculations.

Maintenance Dose of Water
=Total Intake of Water−Abnormal Loss of Water
Maintenance Dose of Sodium
=Total Intake of Sodium−Abnormal Loss of Sodium

Gain or loss of sodium (Na balance) was calculated from the following equation (Fig. 1).

Gain or Loss of Sodium (Na balance)
=Maintenance Dose of Sodium−Urinary Excretion of Sodium

The same calculation was made in the metabolism of potassium and chloride.

Insensible water loss was assumed to be 93.5 per cent of the insensible weight loss,[6),7)] which was calculated as in Fig. 1.

Urinary excretion of solute was calculated by multiplying the urine volume (ml.) by the urine osmolarity (mOsm./L.).

Urinary Excretion of Solute
=Urine Volume (ml.)×Urine Osmolarity (mOsm./L.)

Obligatory urine water was calculated on the assumption that the average maximal concentration of urine is 1,000 mOsm./L. in postoperative periods. The equation is thus,

Obligatory Urine Water (ml.)
=Urinary Excretion of Solute (mOsm.)×1 (ml./mOsm.)

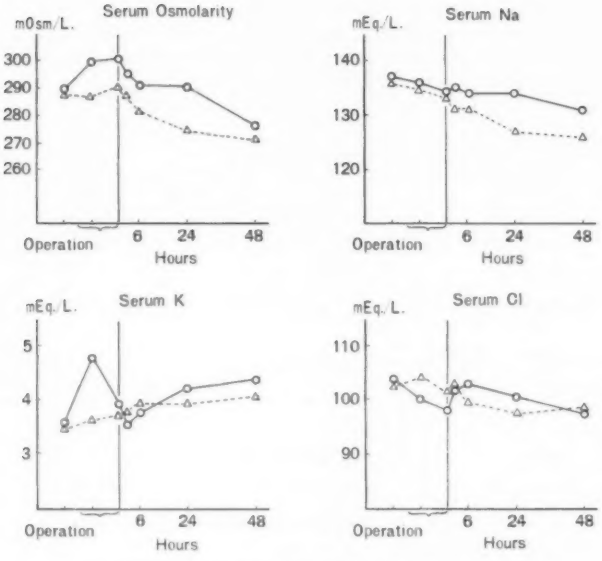
Osmolarity of serum and urine was determined by freezing point depression[8)] with an advanced osmometer. Sodium and potassium were determined by Hitachi photo-electric spectrophotometer, and chloride by Schales and Schales' method.[9)]

Results

Water Metabolism

1) Serum Osmolarity and Serum Na

Serum osmolarity during operation was high in patients with the pump-



○—○ Average of 10 cases operated with pump-oxygenator
△----△ Average of 8 cases operated without pump-oxygenator

Fig. 2. Changes in serum osmolarity and Na, K and Cl concentrations.

Table II. Insensible Water Loss, Obligatory Urine Water and Minimum Requirement of Water

(ml./M.²/day)

	First Postoperative Day			Second Postoperative Day		
	Insensible Water Loss	Obligatory Urine Water	Minimum Requirement of Water	Insensible Water Loss	Obligatory Urine Water	Minimum Requirement of Water
With Perfusion	689± 83*	626±199*	1,045±247*	566±164*	586±104*	882±225*
Without Perfusion	839±196*	631±122*	1,200±236*	747±300*	615±158*	1,091±311*
	755±159*	628±167*	1,114±246*	650±246*	600±128*	980±275*

(* is $\sqrt{U^2}$: U^2 = Universal variation of the sample)

oxygenator (Fig. 2). Postoperatively serum osmolarity as well as serum sodium concentration decreased gradually in both groups. Postoperative decrease of serum Na and osmolarity was larger in patients without perfusion than in those with it.

2) Minimum Requirement of Water

Minimum requirement of water was calculated by the following equation.

$$M.R.W. = I.W.L. + O.U.W. - M.W.$$

,where M.R.W. represents the minimum requirement of water, I.W.L. the insensible water loss, O.U.W. the obligatory urine water and M.W. the metabolic water. Abnormal losses such as naso-gastric suctions were replaced each time by a fluid of the same constitution and so should not be included in calculation of the minimum requirement of water.

The insensible water loss was determined by the calculation above (Fig. 1). As Table II shows, the mean value of insensible water loss in patients without pump-oxygenator was larger than in those with it, but the difference is statistically insignificant.

I.W.L. in the 1st postoperative day	$755 \pm 159^*$ ml./M.^{2}/day
I.W.L. in the 2nd postoperative day	$650 \pm 246^*$ ml./M.^{2}/day

The obligatory urine water was calculated from urinary excretion of solute.

O.U.W. in the 1st postoperative day	$628 \pm 167^*$ ml./M.^{2}/day
O.U.W. in the 2nd postoperative day	$600 \pm 128^*$ ml./M.^{2}/day

Metabolic water was assumed to be 270 ml./M.^{2}/day.[10]

Minimum requirement of water was obtained by substituting into the equation the data above.

M.R.W. in the 1st postoperative day	$1{,}114 \pm 246^*$ ml./M.^{2}/day
M.R.W. in the 2nd postoperative day	$980 \pm 275^*$ ml./M.^{2}/day

The difference in minimum requirement of water between the patients with pump-oxygenator and those without it, or between the first and second postoperative day, was not statistically significant.

3) Upper Limit of Water Intake

The data above refer to the minimum dose of water required. Water intake less than this amount will result in metabolic deterioration from dehydration. So, from a practical standpoint, administration of some excess water is advisable, if it can be done safely.

The interrelation of serum osmolarity and maintenance dose of water is shown in Fig. 3. Serum osmolarity was higher in cases of smaller maintenance doses of water, whereas levels of less than 270 mOsm./L. of serum osmolarity were seen when the maintenance dose of water was larger than 1,400 ml./M.^{2}/day.

Body weight changes and maintenance dose of water are shown in Fig. 4. Body weights without urine in bladder were compared. Weight gains were

* is $\sqrt{u^2} : u^2$ = universal variation of the sample

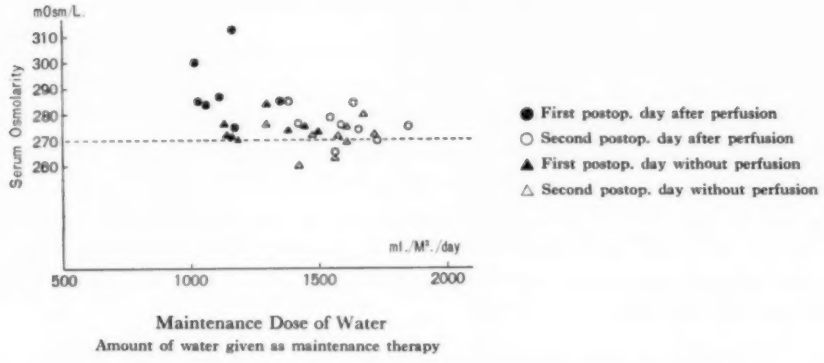


Fig. 3. Relationship between amount of water given and serum osmolarity.

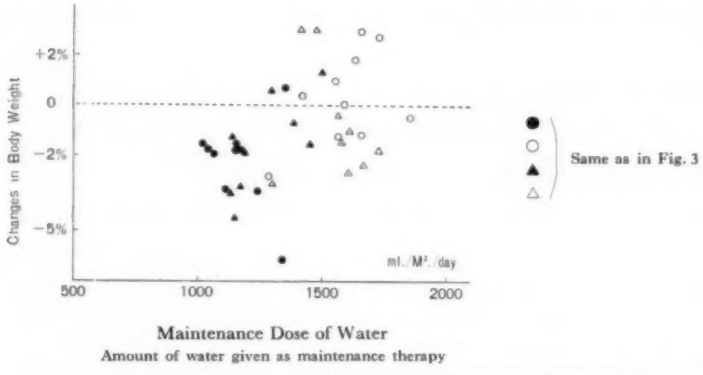


Fig. 4. Relationship between amount of water given and the percentage change in body weight.

observed when the maintenance dose of water was larger than 1,400 ml./M.²/day. It was therefore concluded that water intake should be less than 1,400 ml./M.²/day.

Among the harmful effects of overintake of water, pulmonary edema is most feared after cardiac surgery. In 2 cases of this study, pulmonary edema occurred because of extraordinarily large amounts of blood or fluid administered during operation. During the postoperative course in these cases, water was restricted to 1,339 ml./M.²/day or 1,017 ml./M.²/day and a few hours later pulmonary edema subsided without any recurrence. In the other 18 cases given from 962 ml./M.²/day to 1,859 ml./M.²/day of water, no pulmonary edema was seen. So it was concluded that a water intake of less than 1,400 ml./M.²/day was safe if it was given at approximately the same rate throughout 24 hours.

4) Conclusions

The appropriate maintenance dose of water is 1,100 ml./M.²/day to 1,400 ml./M.²/day in the first postoperative day and 1,000 ml./M.²/day to 1,400 ml./M.²/day in the second postoperative days.

Electrolyte Metabolism

Approximately the same dose of electrolytes were given to both groups with and without extracorporeal circulation.

1) Serum Na, K and Cl Concentration Values

The serum sodium concentration values, which largely reflect water metabolism, were parallel to serum osmolarity and showed a gradual decrease during the first and second postoperative days (Fig. 2).

Serum potassium concentration values in patients without extracorporeal circulation showed a gradual increase during the first and second post-operative days. In children with extracorporeal circulation, serum potassium concentration values were higher during perfusion. They showed slight hypokalemia 2 or 6 hours after operation, but thereafter a gradual increase was observed during the first and second postoperative days (Fig. 2). However, these serum electrolyte values remained within or close to normal range in all subjects.

2) Maintenance Dose and Gain or Loss of Electrolytes

In Fig. 5, interrelations are shown between maintenance dose and gain or loss (=balance) of electrolytes. When the maintenance dose of sodium was larger, sodium accumulation occurred, whereas the balance was negative on smaller maintenance doses of sodium. From these data, it was concluded that

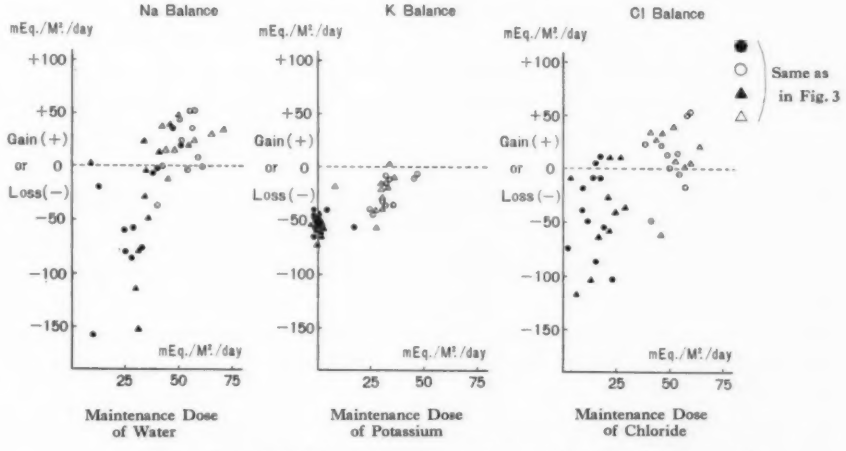


Fig. 5. Relationship between maintenance dose and gain or loss (balance) of sodium, potassium and chloride.

the appropriate dose of sodium is 40–50 mEq./M.²/day, on the assumption that the maintenance dose should be the same as output.

In the first postoperative day, potassium balance showed an average loss of 50 mEq./M.²/day, because no potassium was given during this severely ill period. During the second postoperative day, about 30 mEq./M.²/day of potassium was given, and the potassium balance was still negative. More potassium may be given, but it is difficult to standardize the daily maintenance dose of potassium, because hyperkalemia was often seen in patients with circulatory failure.

Chloride balance in relation to chloride maintenance dose is also shown in Fig. 5. An appropriate dose of 40–50 mEq./M.²/day was concluded on the basis of identical results as those found with sodium metabolism.

Discussion

In 1957, Sturtz and his associates[11] carried out 21 balance studies in children after open heart surgery and gave 493 ml./M.²/day and 765 ml./M.²/day of minimum water requirement (Table III). When the maintenance dose of water is discussed, abnormal losses should be excluded in calculation—there must be clear distinguishment between maintenance therapy and abnormal loss therapy.[11)–13)] So, their data could be regarded as 493 ml./M.²/day and 615 ml./M.²/day of minimum water requirement (minimum maintenance dose of water). Comparing our data with Sturtz's investigation in Table III, a large difference is found especially in insensible water loss and obligatory urine water.

As for insensible water loss calculated in this investigation, the following 2 factors have to be kept in mind.

1) Younger children were studied.
2) Oxygen tents with 70–85 per cent humidity were employed, whereas

Table III. Minimum Requirement of Water

	Data in This Investigation		Sturtz et al.[11]	
	First Postoperative Day	Second Postoperative Day	First Postoperative Day	Second Postoperative Day
(1) Insensible Water Loss	755	650	469	420
(2) Obligatory Urine Water	628	600	294	465
(3) Abnormal Losses	—	—	0	150
(4) Metabolic Water	270	270	270	270
(5) Minimum Requirement of Water	(5)=(1)+(2)−(4) 1,114	980	(5)=(1)+(2)+(3)−(4) 493	765

(ml./M.²/day)

in Sturtz's studies[1] the tent was filled with water mist.

Insensible water loss obtained in this investigation is more physiological and more closely approximates to Heeley-Talbot's equation.[14]

Obligatory urine water reflects urinary excretion of solute. Even with appropriate deduction of solute intake due to low-electrolyte solution used in this investigation, urinary excretion of solute in the first postoperative day is much larger than that in Sturtz's studies.[1] This probably is explained by the difference in the methods of the perfusion, such as hemodilution, rate of perfusion and so forth.

With these considerations, it is found that the minimum requirement of water varies with the age of the patient, humidity in the oxygen tent, method of perfusion and solutions used in parenteral fluid therapy, and so it should be determined in each Cardiovascular Surgical Unit respectively. The minimum requirement of water discussed above should be considered to be the lower limit from a clinical standpoint. Some patients, who were given water in amounts close to the minimum requirement, not only complained of severe thirst, but also demonstrated clinical sings of dehydration in skin and oral mucosa. In small children, who need adequate hydration, the maintenance dose of water should be near 1,400 ml./M.^{2}/day. As was shown in this investigation, on a maintenance dose of water near 1,400 ml./M.^{2}/day, no postoperative pulmonary edema developed. From the standpoint of water metabolism, there must be clear distinguishment between the postoperative cardiac patients with good cardiac output and those with circulatory failure. The latter can be diagnosed by urine volume, urinary osmolarity and clinical signs.[15),16] If circulatory failure is ruled out, it is safe and advisable to use maintenance doses of water up to 1,400 ml./M.^{2}/day.

Postoperative hyponatremia-hyperkalemia was observed in this investigation (Fig. 2). This seems to correspond to the post-traumatic Na-K shift[17] noted in general surgery. Although the precise mechanism of this hyponatremia is not clearly understood, dilution by sodium free metabolic water and low electrolyte parenteral fluid is thought to be of primary importance. For example, if we had used only 5 per cent glucose solution in these balance studies, more marked hyponatremia supposedly would have been seen. So it was felt advisable to use some sodium postoperatively. As has been demonstrated in postoperative patients after general surgery,[18] increased intake of sodium will cause sodium accumulation, whereas negative balance occurs if the parenteral sodium dose is too little. In this investigation it was found that parenteral administration of 40–50 mEq./M.^{2}/day of sodium does not cause negative or positive balance and sodium intake up to 40–50 mEq./M.^{2}/day seems to be a safe and advisable dose.

References

1. Sturtz, G. S., Kirklin, J. W., Burke, E. C., and Power, M. H.: Circulation **16**: 988, 1957.
2. Schmidt-Mende, v. M.: Thoraxchirurgie **9**: 90, 1961.
3. Norberg, B., Senning, A., and Tomaszewski, W.: Acta Chir. Scand. **120**: 237, 1960.
4. Ebert, P. A., Jude, J. R., and Gaertner, R. A.: Circulation **31**: Suppl. 137, 1965.
5. DuBois, D. and DuBois, E. F.: Arch. Int. Med. **17**: 863, 1916.
6. Levine, S. Z. and Marples, E.: Am. J. Dis. Child. **40**: 269, 1930.
7. Newburgh, L. H. and Johnston, M. W.: Physiol. Rev. **22**: 1, 1942.
8. Crawford, J. D. and Nicosia, A. P.: Lab. Clin. Med. **40**: 907, 1952.
9. Schales, O. and Schales, S. Z. J.: J. Biol. Chem. **140**: 879, 1941.
10. Talbot, N. B., Crawford, J. D., and Butler, A. M.: New Eng. J. Med. **248**: 1100, 1953.
11. Butler, A. M. and Talbot, N. B.: New Eng. J. Med. **231**: 585, 1944.
12. Holliday, M. A. and Seger, W. E.: Pediatrics **19**: 823, 1957.
13. Nakajo, T., Ishida, M., Saito, S., Sawaguchi, S., Sato, T., Hanawa, M., Hori, T., and Tsuchida, Y.: presented on the 11th International Congress of Pediatrics, Tokyo, Japan, 1965.
14. Heeley, A. M. and Talbot, N. B.: Am. J. Dis. Child. **90**: 251, 1955.
15. Grismer, J. T., Levy, M. J., Lillehei, R. C., Indeglia, R., and Lillehei, C. W.: Surgery **55**: 24, 1964.
16. Grismer, J. T., Rozelle, L. T., and Koch, R. B.: Dis. Chest **49**: 467, 1966.
17. Moore, F. D.: Metabolic Care of Surgical Patient. W. B. Saunders Co., Philadelphia, 1959.
18. Border, J., Talbot, N. B., Terry, M., and Lincoln, G.: Metabolism **9**: 897, 1960.

Hemodynamic Effects of Propranolol in Patients with Fallot's Tetralogy at Rest

Kenji Ito, M.D., Akira Furuse, M.D., Sohgen Boku, M.D., *and* Masahiro Saigusa, M.D.

Summary

The hemodynamic effects of propranolol at rest were studied in 13 patients with Fallot's tetralogy. After the infusion of propranolol into right ventricle, heart rate and blood pressure decreased in all cases, whereas there were no definite tendencies in changes of right ventricular pressure, its first derivative, and arterial oxygen saturation. The results obtained indicated that propranolol has little, if any, effects in relieving the right ventricular outflow tract obstruction in Fallot's tetralogy at rest. The changes of arterial oxygen saturation depend mainly on the changes of total peripheral resistance. It is concluded that the role of sympathetic activity in producing cyanosis at rest in Fallot's tetralogy is minimal.

Additional Indexing Words :

Heart rate Blood pressure Right ventricular pressure Right ventricular dp/dt Arterial oxygen saturation Angiocardiography Dye dilution curve Total peripheral resistance

THE effects of beta-adrenergic blockade on relieving anoxic spells in Fallot's tetralogy have been studied in recnet years,[1)–5)] suggested by the fact that beta-adrenergic blockade was useful in relieving functional left ventricular outflow obstruction in idiopathic hypertrophic subaortic stenosis.[6)] Further, the effects of beta-adrenergic blockade in exercise,[3)] beta-adrenergic stimulation with isoproterenol,[3),4)] or operative intervention[7)] have been evaluated and the same effects of relieving right ventricular outflow tract obstruction have been reported. Above mentioned reports, however, have their common denominator in studying the effects of beta-adrenergic blockade under certain stresses. It seems reasonable that in sympathomimetic state, beta-adrenergic blockade relieves the functional constriction of right ventricular outflow tract. This report concerns the hemodynamic effects of propranolol at rest in Fallot's tetralogy.

From the Department of Thoracic Surgery, Faculty of Medicine, University of Tokyo, Tokyo.

Received for publication Jnly 22, 1968.

Table I

		Propranolol (mg./Kg.)	Heart Rate (min.)	Blood Pressure (mm.Hg)	R.V. Pressure (mm.Hg)
1. T. I. 6. M.	B	0.05	136	110/76	116/0-15
	A		115	92/72	120/-20-22
2. J. M. 10. M.	B	0.2	94	84/38	97/10-14
	A		73	76/46	102/13-17
3. K. N. 7. M.	B	0.2	91	104/76	192/20-23
	A		86	94/76	187/20-
4. M. N. 11. M. Blalock's Op.	B	0.1	125	120/76	120/14-19
	A		105	112/72	119/0-14
5. N. I. 12. M.	B	0.2	78	98/70	105/5-17
	A		67	90/70	86/9-12
6. K. K. 13. M. Blalock's Op.	B	0.1	97	118/90	116/16
	A		81	114/88	130/-11-19
7. K. S. 14. M. Blalock's Op.	B	0.1	86		132/15-23
	A		73		119/10-20
8. S. O. 16. F. Blalock's Op.	B	0.2	70	141/98	140/0-16
	A		49	130/98	140/-14-13
9. S. K. 17. M. Blalock's Op.	B	0.2	73	134/64	120/0-20
	A		42	124/54	113/3-20
10. K. F. 24. F. Blalock's Op.	B	0.2	65	108/76	112/11-17
	A		57	104/78	114/11-17
11. S. K. 24. F. Blalock's Op.	B	0.2	66	135/78	140/17-22
	A		60	120/75	136/13-17
12. K. T. 25. M.	B	0.1	67	160/120	
	A		54	160/114	
13. T. M. 29. M.	B	0.00	60	106/82	
	A		52	100/80	

R.V. Peak dp/dt (mm.Hg/sec.)	Oxygen Saturation		Peripheral Resistance (dynes·sec·cm.$^{-5}$)	Patterns of Right Ventricular Outflow Tract Obstruction
	Arterial (Vol.%)	Venous (Vol.%)		
1,230	91.0	71.2	1,660	Valv. P.S. (+) Intermediate Inf. P.S.
1,450	83.4	71.0	935	
3,061	76.3	46.4	933	Valv. P.S. (+) Localized Inf. P.S.
2,078	79.7	38.2	1,239	
1,845	89.3	73.1	2,241	Valv. P.S. (+) Tubular Inf. P.S.
1,640	88.4	60.0	2,110	
1,950	91.2	83.0	1,092	Valv. P.S. (+) Localized Inf. P.S.
1,950	91.6	82.3	1,658	
2,932	68.5			Valv. P.S. (−) Tubular Inf. P.S.
1,373	73.2			
780	81.5	67.0	1,088	Valv. P.S. (−) Localized Inf. P.S.
1,527	77.0	67.0	631	
1,920	71.5	59.5		Valv. P.S. (−) Localized Inf. P.S.
1,320	72.0	53.0		
1,670	84.0	68.1	2,184	Valv. P.S. (+) Intermediate Inf. P.S.
2,295	88.1	66.7	2,354	
2,455	86.1	71.5	1,572	Valv. P.S. (−) Localized Inf. P.S.
1,664	86.1	71.9	1,080	
1,508	76.4			Valv. P.S. (+) Intermediate Inf. P.S.
1,830	76.4			
1,488	78.0	60.7	951	Valv. P.S. (+) Tubular Inf. P.S.
1,296	80.5	61.1	1,107	
	83.0			Valv. P.S. (+) Tubular Inf. P.S.
	89.1			
	92.1			Valv. P.S. (+) Localized Inf. P.S.
	91.9			

Methods

Thirteen patients with Fallot's tetralogy, including one case with previous Brock's valvotomy and 6 cases with Blalock's anastomoses, ranging in age from 6 to 29 years, were subjected to study. After routine selective angiocardiography, propranolol, from 0.05 to 0.2 mg. per Kg. body weight, was infused into right ventricle. Heart rate, blood pressure, right ventricular pressure and its first derivative, and oxygen saturation of arterial and venous blood were measured before and 10 min. after the administration of propranolol. In 2 cases, dye dilution curves were obtained and the changes of right-to-left shunt were estimated. The hemodynamic results obtained were correlated with the types of right ventricular outflow tract obstruction evaluated angiocardiographically and/or by operative findings.

Results

Full data are presented in Table I.

1) Heart rate: In all cases, heart rate decreased from 5.5 to 42.3% of control values (Fig. 1).

2) Blood pressure: In all but one, blood pressure fell from 4 to 16.5% of control values (Fig. 1).

3) Right ventricular pressure: Right ventricular systolic pressure unchanged in one case, decreased in 6 from 0.7 to 18%, and increased in 4 from 2 to 12% of control values (Fig. 2). Right ventricular end-diastolic pressure unchanged in 6, and increased in 3.

4) First derivatives of right ventricular pressure: Peak dp/dt of right ventricular pressure unchanged in one case, decreased in 6 from 11 to 53%, and

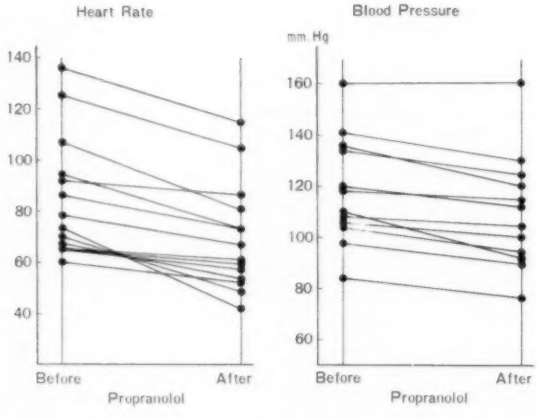


Fig. 1

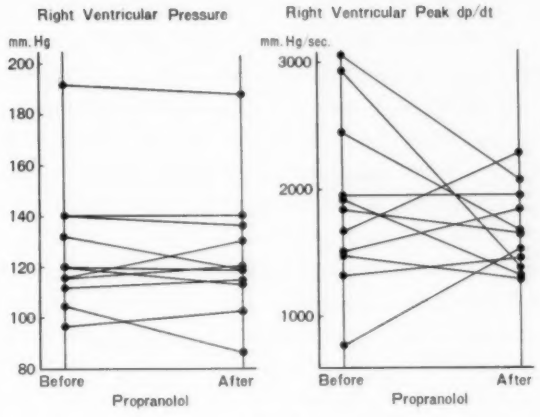


Fig. 2

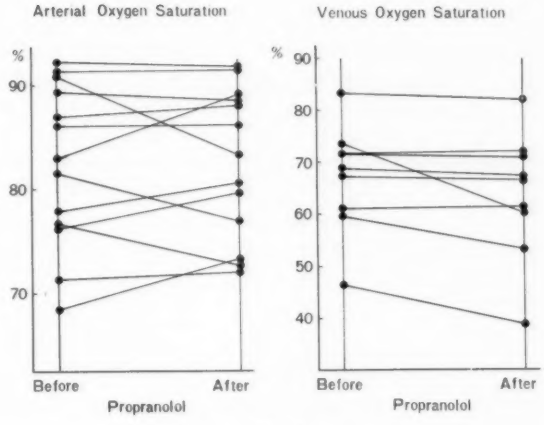


Fig. 3

increased in 4 from 9.7 to 96% of control values (Fig. 2). The negative peak dp/dt of right ventricular pressure unchanged in 2 cases, decreased in 4 from 5.2 to 37.5% and increased in 5 from 8.3 to 71.2% of control values.

5) Isometric contraction time of right ventricle: The right ventricular isometric contraction time unchanged in 5 cases, shortened in 1, and prolonged in 5.

6) Arterial oxygen saturation: Arterial oxygen saturation unchanged in one case, increased in 7 from 0.4 to 7.3%, and decreased in 5 from 0.2 to 8.5% of control values (Fig. 3).

7) The oxygen saturation of right ventricle unchanged in 1 case,

Control R−L Shunt 22 %
Sao_2 91.2 %

Propranolol R−L Shunt 28 %
Sao_2 91.9 %

Fig. 4

Table II. Relation of the Types of Right Ventricular Outflow Obstruction and the Response to Propranolol

	Infundibular			Valvular Stenosis	
	Localized	Intermediate	Tubular	+	−
Responsive	4	1	2	5	2
Non-responsive	3	3	0	4	2

increased in 4, and decreased in 7 (Fig. 3).

8) Total peripheral resistance decreased in 4 cases from 6 to 43.7%, and increased in 6 from 8 to 51.5% of control values.

9) Dye dilution curves: Right-to-left shunt increased 27% of control value in 1 case (Fig. 4), and essentially unchanged in another.

10) The types of right ventricular outflow tract obstruction: As shown in Table II, there is no definite relationship between the types of right ventricular outflow tract obstruction and the effect of propranolol.

Discussion

In considering the mechanisms of hemodynamic changes by any drugs, it seems necessary to know the fundamental intracardiac pressure and flow relationships. Levine et al.[8] demonstrated from their studies on the instan-

taneous pressure-flow relationships across the ventricular septal defect in tetralogy of Fallot that the right-to-left shunt occurred at 2 phases and 2 sites during the cardiac cycle ; namely, during early ventricular ejection into the aorta, and during isovolumic ventricular relaxation directly across the ventricular defect into the left ventricle, and left-to-right gradients and shunting across the defect occurred during isovolumic ventricular contraction and during diastole. The mechanisms of decreasing right-to-left shunt by beta-adrenergic blockade are considered to result from the increase in left-to-right pressure gradients during isovolumic contraction and diastole, and the decrease or the inversion of left-to-right pressure gradients during early ventricular ejection and isovolumic relaxation. The results obtained from our studies, namely, the elavation of right ventricular pressure during early ventricular ejection, the prolongation of ejection phase and sometimes the abnormal elevation of end-diastolic pressure in some cases after the administration of propranolol shows the unfavorable effects in order to decrease right-to-left shunt. Contrariwise, the increase of relaxation velocity during isovolumic relaxation has favorable effect on increasing left-to-right shunt. In other way, relation of the changes of arterial oxygen saturation to the changes of right

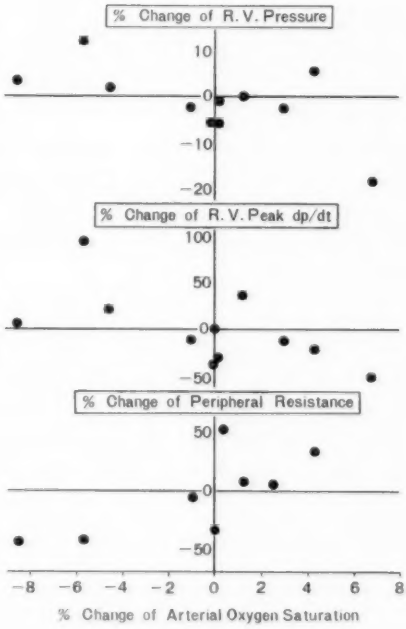


Fig. 5

ventricular systolic pressure, right ventricular peak dp/dt and total peripheral resistance was evaluated. As the increase of right ventricular systolic pressure and its peak dp/dt and the decrease of total peripheral resistance are to increase right-to-left shunt and consequently decrease the arterial oxygen saturation, whereas the decrease of right ventricular systolic pressure and its peak dp/dt and the increase of total peripheral resistance decrease right-to-left shunt, there must be negative correlation between the changes of right ventricular systolic pressure and its peak dp/dt and the changes of arterial oxygen saturation, and positive correlation between changes of total peripheral resistance and those of arterial oxygen saturation. As shown in Fig. 5, the effect of beta-adrenergic blockade in relieving cyanosis is considered to be most dependent on the increase of total peripheral resistance. The fact that the natural fluctuation in the degree of cyanosis at rest in Fallot's tetralogy ranges from -19.4 to $+14.6\%$ in arterial oxygen saturation should be taken into consideration when evaluating the pharmacologic effects. The increase of arterial oxygen saturation after the administration of beta-adrenergic blockade were within 10% in most reported cases.

References

1. Cumming, G. R. and Carr, W: Lancet **i**: 519, 1966.
2. Cumming, G. R. and Carr, W.: Am. Heart J. **74**: 29, 1967.
3. Shah, P. M. and Kidd, L.: Am. J. Cardiol. **19**: 653, 1967.
4. Kato, H., Hirose, M., Yamaguchi, M., Yoshizawa, Y., Fukuda, H., Oda, T., and Nagayama, T.: Jap. Circulat. J. **31**: 1855, 1967.
5. Honey, M., Chamberlain, D. A., and Howard, J.: Circulation **30**: 501, 1964.
6. Harriosn, D. C., Ross, J., Click, C., Chidsey, C. A., and Braunwald, E.: Clin. Res. **11**: 167, 1963.
7. Asano, K.: Jap. Heart J. **7**: 513, 1966.
8. Levine, A. R., Boineau, J. P., Spach, M., Canent, R. V., Jr., Capp, M. P., and Anderson, P. A. W.: Circulation **34**: 4, 1966.

Reversed Splitting of the Second Heart Sound in Arterial Stenotic Lesions

Tsuguya SAKAMOTO, M.D., Tetsuro YAMADA, M.D.,
Zen'ichiro UOZUMI, M.D., Sheng Yu CHANG, M.D.,
Hidezo NAKAMURA, M.D., *and* Hideo UEDA, M.D.

SUMMARY

The behavior of the splitting of the second heart sound was analyzed in 78 cases with peripheral arterial stenosis, including 51 of " aortitis syndrome " (Takayasu's arteritis).

Reversed or paradoxical splitting was observed in 10 cases of aortitis syndrome and 1 case with renal artery stenosis. Frequent occurrence of the reversed splitting was observed in " extensive " form of aortitis syndrome (8 out of 18 cases, i.e. 44%).

Correlative study disclosed that the reversed splitting was frequently associated with gallop rhythm and exaggerated " a " wave as well as systolic bulge in the precordial low-frequency tracing (particularly the apex cardiogram). Frequent coincidence between the reversed splitting and aortic regurgitation was observed in aortitis syndrome (8 out of 17 cases with aortic insufficiency). Cardiac enlargement on the chest roentgenogram and the electrocardiographic left ventricular hypertrophy and ischemic change as well as QT prolongation were frequently present in cases with reversed splitting.

The mechanism of the reversed splitting in peripheral arterial stenotic lesion was discussed.

Additional Indexing Words :
Auscultation Phonocardiography Aortitis syndrome (Takayasu's arteritis) Renovascular hypertension Myocardial incompetence QT prolongation

REVERSED or paradoxical splitting of the second heart sound was first described by Wolferth and Margolies[1] in cases with complete left bundle branch block. Subsequently, various electrical as well as hemodynamic conditions have been proposed to cause the reversed splitting.[2)–5)]

Since 1961, the occasional incidence of the reversed splitting of the second

From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

Presented at the 46th Kanto-Koshinetsu-Hokuriku Regional Meeting of the Japanese Circulation Society in September 23, 1967.

Received for publication August 10, 1968.

heart sound in cases with peripheral arterial stenotic lesion has been noticed and sporadically published.[6)–9)] In the present study, the real incidence of this phenomenon was estimated by cumulative materials and the associated clinical findings were analyzed to search for the additional information regarding the genesis of the reversed splitting.

Materials and Methods

Phonocardiographic, phonoarteriographic and angiographic studies were performed in a total of 78 cases with arterial stenotic lesion, including 51 of aortitis syndrome (Takayasu's arteritis). Their age distribution was varied from 9 to 66 years with an average of 32.3, and sexual difference was 18 male and 60 female. Phonocardiograms and phonoarteriograms were recorded using dynamic microphone and multi-filter system phonocardiograph as previously illustrated.[9)–11)] Identification of the two components of the second heart sound was made on the simultaneous tracings from various auscultatory areas taken during spontaneous respiration. All cases with reversed splitting had unequivocal 2 components of the second heart sound, which were separated each other from 0.02 to 0.04 sec. in expiration. Carotid pulse tracing was taken in many cases. Aortography as well as selective arteriography were performed injecting the dye (Angio-Conray) via catheter inserted to the aorta by Seldinger's technique or translumbar puncture to examine the exact location and the severity of the stenotic changes in aorta and its branches. Evaluation of the clinical data was mainly made on the auscultation and phonocardiograms, chest roentgenograms, and electrocardiograms.

Results

Incidence of reversed splitting of the second heart sound (Table I):

Reverved splitting was observed in 11 out of 78 cases (14.1%). Ten of these 11 had aortitis syndrome as the underlying disease. These 10 corresponded to one-fifth of the cases with aortitis syndrome examined (19.6%). In various forms of this syndrome, however, extensive form, in which both thoracic and abdominal aorta and their branches were involved, showed the highest incidence of 44.4%, i.e., 8 out of 18 cases had the reversed splitting. In the other forms of aortitis syndrome the reversed splitting was less frequent, and so was it in the stenotic arterial lesions other than aortitis syndrome. Renovascular hypertension alone was the infrequent cause of the reversed splitting (1 out of 16 cases ; 6.3%).

In regard to the age, the reversed splitting was not observed in 11 cases below the age of 20. However, each decade over 20 years had almost equal incidence of this abnormal splitting.

Clinical observations (Table II):

Gallop rhythm: The group with reversed splitting frequently had gallop

Table I. Incidence of Reversed Splitting of the Second Heart Sound

	Reversed Splitting	
	Present	Absent
1. Age		
9–20 yrs.	0	11 cases
21–40 yrs.	7	37
41–66 yrs.	4	19
2. Classification of underlying disease		
A. Aortitis syndrome (51 cases)		
Extensive form*	8	10
Aortic arch form	2	27
Coarctation form	0	4
B. Other than aortitis syndrome		
Coarctation of the aorta	0	4
Kinking of the aorta	0	2
Renal artery stenosis*	1	15
Others	0	5
	11	67

* Cases with renal artery stenosis and aortitis syndrome (6 cases) were classified in the group of extensive form of aortitis syndrome.

rhythm. In a half of cases, quadruple rhythm was noticed. At the same time, prominent "a" wave and systolic bulge in the apex cardiogram were often observed in such cases. On the other hand, 55 out of 67 cases without reversed splitting had no gallop sound.

Aortic insufficiency: Though the degree of the regurgitation is not so heavy, aortic insufficiency was observed in one-third of the cases with aortitis syndrome (17 out of 51 cases). Of these 17, 8 cases had reversed splitting, whereas only 3 out of 61 cases without aortic insufficiency showed reversed splitting.

Chest roentgenogram: Though the small heart may have reversed splitting, general tendency was the high incidence in cases with large heart.

Electrocardiogram: Reversed splitting was always accompanied by significant left ventricular hypertrophy and strain, and ischemic change was observed in a half of cases with reversed splitting. Except one, T wave in the left precordial leads (V_5–V_6) was inverted or at least flat, and Q-T interval was prolonged in most cases with reversed splitting. Thus QTc was ranged from 0.438 to 0.541 except 1, whereas the QRS duration was normal in all. On the other hand, QT prolongation was observed in only 21 out of 67 cases without reversed splitting and, furthermore, all these 21 but 2 cases had single second heart sound without demonstrable respiratory splitting. One of the 2 exceptional cases was the case of congenital coarctation of the aorta complicated by

Table II. Clinical Data and Reversed Splitting of the Second Heart Sound

	Reversed Splitting Present	Absent
1. Gallop rhythm		
Quadruple	6	1 cases
Third sound	2	7
Atrial sound	3	4
None	0	55
2. Aortic insufficiency		
Present	8	9
Absent	3	58
3. Cardiomegaly*		
++ (CTR≥60%)	4	2
+ (60%>CTR≥50%)	5	19
None (CRT<50%)	2	38
4. Electrocardiogram**		
Left ventricular hypertrophy myocardial insufficiency	5	3
Left ventricular hypertrophy	5	6
Nonspecific ST·T change	0	9
Others	0	3
Normal	0	39

* Chest roentgenograms of 9 cases were not available or were not suitable for the study.

** Twelve-lead electrocardiogram was available in 70 cases.

atrial septal defect (autopsy confirmed) and incomplete right bundle branch block, and this had fixed splitting. Normal QT interval was observed in the remainder cases, and two-thirds of which had usual respiratory splitting of the second heart sound.

Blood pressure: Though the central aortic root pressure was not obtained in almost all cases, the highest level of blood pressure in the extremities at the time of the phonocardiographic examination was correlated with the presence or absence of reversed splitting. No close correlation was confirmed in relation to both systolic and diastolic pressure levels.

Illustrative Cases

Case 1, T. N., 35-year-old female with extensive form of aortitis syndrome. Aortogram showed marked irregularity of the wall and the reduced caliber of the abdominal aorta, and the corresponding arterial stenotic murmur was observed over the affected site (Fig. 1, below left). Though the aortography in the aortic arch was missed, physical examination revealed moderate stenosis of both carotid arteries and severe left and moderate right subclavian arterial stenoses. The blood pressure in

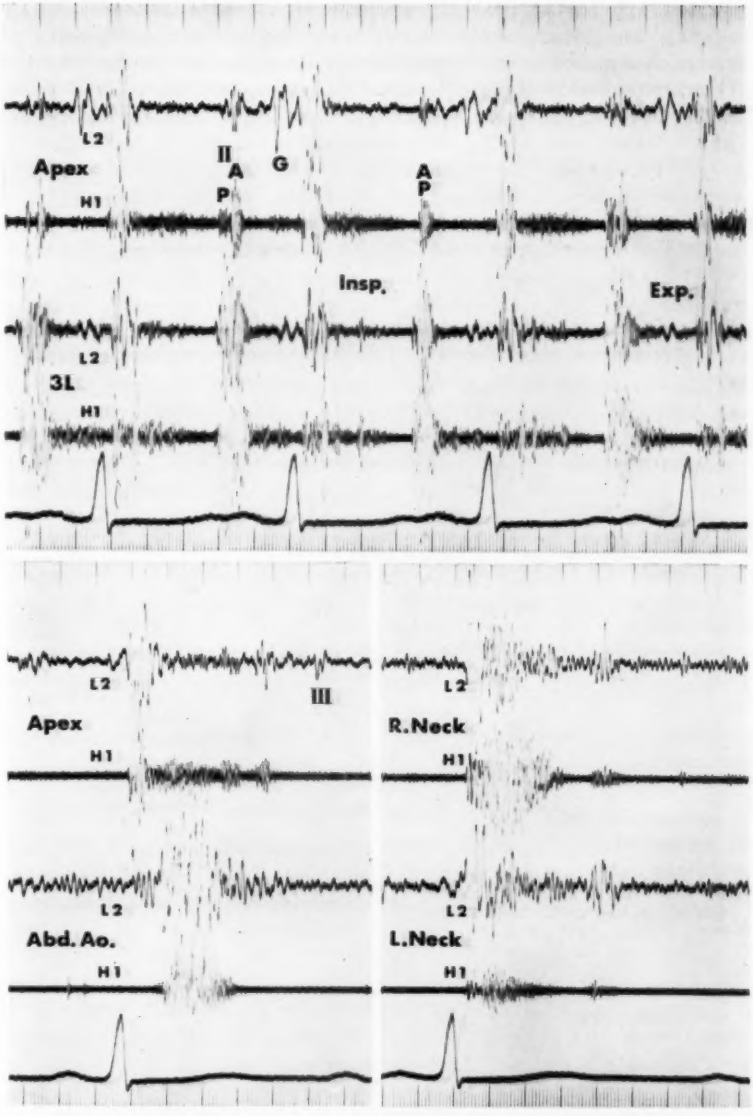


Fig. 1. Phonocardiograms of case 1. Symbols IIA and IIP represent aortic and pulmonic component of the second heart sound. In this case, basal IIP is accentuated, so that it is inscribed even in the apical phonocardiogram as a definite, but smaller, vibration. Gallop sound (G) is mainly due to the third heart sound (III). L=low frequency, M=medium frequency, and H=high frequency phonocardiograms (details: see reference 10). Paper speed: 100 mm./sec. Time lines: 0.1 and 0.01 sec.

the right arm was 110/70, whereas it could not be measured in the left and the pulse was absent. The blood pressure in the lower extremities was 186/64 or 178/62. Stenotic arterial murmurs were identified over both carotid arteries (Fig. 1, below right) and over both subclavian arteries. Concomitant aortic insufficiency was noticed by the faint but characteristic blowing diastolic murmur best recorded in

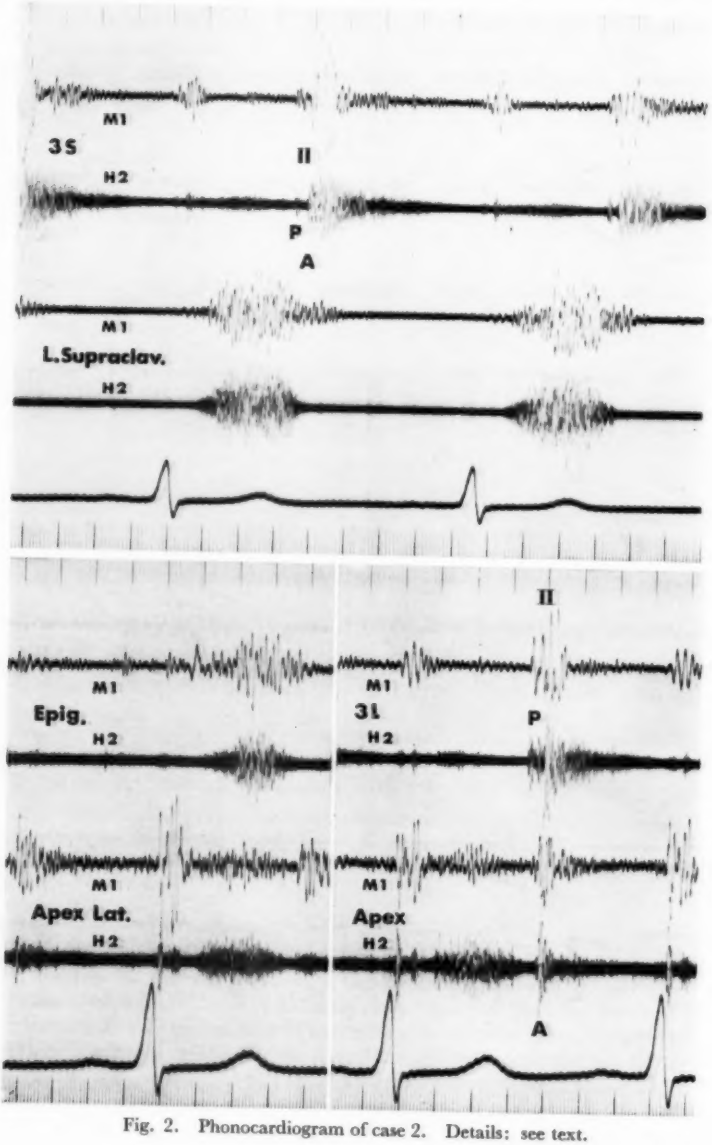


Fig. 2. Phonocardiogram of case 2. Details: see text.

the 3rd left interspace (Fig. 1, top). Besides these, precordial phonocardiograms revealed the apical third heart sound, which occasionally gave summation gallop, aortic ejection sound, accentuation of both components of the second heart sound and the marked *reversed splitting* (Fig. 1, top). The split interval between IIP and IIA (pulmonic and aortic components) was 0.04 sec. during expiration and 0.02 sec. during inspiration, though the auscultation revealed the split second sound only during expiratory phase. This patient had moderate cardiomegaly (cardiothoracic ratio=55%), and the electrocardiogram showed marked left ventricular hypertrophy with ischemic change and prolongation of Q-T interval (QTc=0.508).

Case 2, M. N., 21-year-old female with extensive form of aortitis syndrome. Aortogram showed several stenoses in thoracic and abdominal aorta and the wall was irregular. Between the stenoses slight dilatation of the aorta was present. Ascending aorta was also slightly dilated and the wall had irregular configuration. There was regurgitation of the contrast media into the left ventricle (aortic insufficiency). The origin of left subclavian artery was moderately stenosed, giving a loud stenotic murmur with thrill (Fig. 2, top; L. Supraclav.). Innominate artery had irregular wall, initial portion of the right carotid artery had kinking, and both left common carotid and right vertebral arteries showed narrowing. Blood pressure was 176/20–0 in the right arm, 86/66 in the left and 154/34–0 in the lower extremity. Phonoarteriograms confirmed the stenotic murmurs corresponding to the degree of stenosis of each artery. The murmur of aortic insufficiency was of grade II/VI, best recorded in the 3rd interspace over the sternum (Fig. 2, top). There were atrial and third heart sounds in the apical low frequency phonocardiogram (not shown in this figure). Aortic ejection sound was recorded from base to apex. The *reversed splitting* of the second heart sound was conspicuous and the IIP–IIA interval was 0.03 sec. in expiration. Simultaneous tracing from apex (where the sole IIA is recorded) and 3L (3rd left interspace, where the IIP is best recorded) readily indicates the paradoxically situated both components (Fig. 2, below right). The cardiac size of this case was within normal limit (cardiothoracic ratio=48%), but the electrocardiogram showed marked left ventricular hypertrophy. The QTc was 0.450.

Case 3, Y. S., 24-year-old female with extensive form of aortitis syndrome (aortic arch form with renal artery stenosis) and transient cerebral blindness. Though aortogram demonstrated minimal change in the thoracic aorta, the branches had irregular wall, the carotid arteries were slightly stenosed, and the left subclavian artery was completely occluded. Moreover, left renal artery had localized narrowing in its origin and had poststenotic dilatation. Blood pressure was 170/100 in the right arm, 174/110 in the lower extremities, whereas it could not be obtained in the left arm. The stenotic carotid murmur was observed with thrill as indicated by fine vibrations on the right carotid pulse tracing (Fig. 3, top; R. Car.). There was grade I/VI continuous high-pitched murmur in the left upper quadrant of abdomen, indicating the stenosis of the left renal artery. Precordial auscultation and phonocardiogram revealed a marked quadruple rhythm (Fig. 3, below), distinct apical thrust with prominent " a " wave (ACG), aortic ejection sound and metallic second heart sound with the reversal of the 2 components. Comparison of the tracings from 2R (2nd right interspace, where the IIA is mainly inscribed) and 3L (3rd left interspace, where both components are inscribed) indicated the presence of the reversed splitting, and both components were inscribed well before the

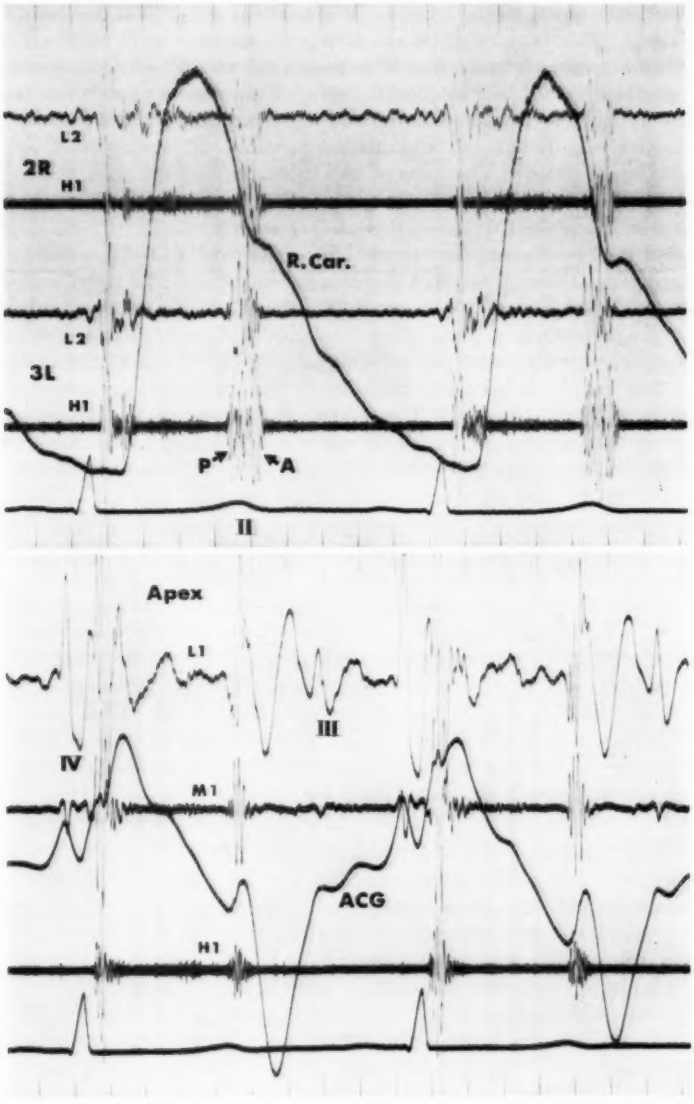


Fig. 3. Phonocardiogram, carotid pulse tracing and apex cardiogram of case 3. Details: see text.

incisura of the carotid pulse tracing. This case had cardiomegaly (cardiothoracic ratio=53.6%), and the electrocardiogram showed the left ventricular hypertrophy and ischemic change in the left precordial leads and the marked prolongation of QT interval (QTc=0.535).

Discussion

As shown in the elaborated study of Gray,[2] reversed splitting of the second heart sound is most frequently observed in complete left bundle branch block, aortic stenosis and patent ductus arteriosus. Occasional incidence was also documented in each case of systemic hypertension as well as mitral stenosis. Later on, many conditions responsible for the genesis of reversed splitting have been proposed (Table III). It is obvious that some of the causes listed (e.g. I

Table III. Genesis of Reversed Splitting of the Second Heart Sound

I. Electrical
  1. Left bundle branch block[1]
  2. Right ventricular premature beat[3),4),12),13)]
  3. WPW syndrome (B type)[3),5),14),15)]
  4. Pacing from right ventricle[13)]
  5. Complete right bundle branch block in the presence of transpostion of great vessels[16)]

II. Hemodynamic
  A. Left ventricular pressure loads
    1. Outflow obstruction
      a. valvular
      b. subvalvular } aortic stenosis[2),17)-20)]
      c. supravalvular
    2. Idiopathic hypertrophic subaortic stenosis[21),22)]
    3. Coarctation[23),24)]
    4. Systemic hypertension[2),4),25)-27)]
    5. Acutely induced increase in systemic resistance[28)]
  B. Left ventricular volume loads
    1. Left-to-right shunt
      a. Patent ductus arteriosus[2)]
      b. Aorto-pulmonary window[5)]
      c. Anomalous systemic venous return[5)]
    2. Aortic insufficiency[23),29)]
  C. Left ventricular dysfunction
    1. Myocardial infarction[30)-32)]
    2. Coronary insufficiency[30),33)]
    3. Left ventricular failure[5),27)]
    4. Primary myocardial disease (amyl nitrite inhalation)[34)]
    5. Anesthesia (sodium pentobarbital)...dog[35)]
  D. Diminished or increased resistance to right ventricular ejection
    1. Tricuspid insufficiency[3),5)]
    2. Tetralogy of Fallot[36)]
    3. Congenital tricuspid stenosis[37)]
    4. Eisenmenger syndrome[38)]
    5. Mitral stenosis[2)]

and IID) do not need to be taken into account to discuss the most probable mechanism of the mode of production of the reversed splitting under discussion.

All 11 cases reported in the present study have one or more conditions listed in Table III. Of these, systemic hypertension, aortic insufficiency and probable myocardial incompetence are thought to be important contributing factor and deserves to be discussed in some detail.

Gray[2] has already pointed out that hypertensive heart disease may have reversed splitting but this is exceptional in this condition. Though Leatham[4] stated that this physical sign is quite common in systemic hypertension, particularly in the systolic variety, our experience[39] did not coincide with his observation. Barlow and Kincaid-Smith[40] gave no statement about the splitting of the second heart sound in their extensive auscultatory and phonocardiographic study of hypertension. Systemic hypertension *per se*, as stated by some authors,[25]–[27] gives either single second sound or narrowly split sound with usual sequence of the 2 components. In the elderly or the aged single second sound is common, and the younger cases usually have the pulmonic component just behind the aortic component. In fact, reversed splitting in systemic hypertension is rare unless there is an associated left ventricular failure.[5],[26],[27] In aortitis syndrome presented in this study, hypertension of moderate degree was observed in many cases. However, the incidence of reversed splitting had no definite correlation to the height of the blood pressure. Certainly, the indirect measurement of the blood pressure may not have a significance to estimate the height of central aortic pressure, but the high incidence of abnormal reversed splitting in aortitis syndrome can not be explained solely by the hypertension co-exists.

Hemodynamically, peripheral arterial stenotic lesion may have a net effect to the left ventricle similar to coarctation of the aorta, particularly when the stenosis is multiple and the degree is grave. Aortitis syndrome often has the stenotic lesion in the descending aorta and it is sometimes a sole pathology (atypical coarctation[41],[42]). However, reversed splitting in coarctation of the aorta is also rare phenomenon, unless the hypertension is marked or severe degree of aortic stenosis is associated.[24] In the present study, none of the 8 cases of either congenital or atypical coarctation had reversed splitting. The reported 2 cases from our country, in which reversed splitting was observed,[23] therefore, remain a possibility of aortitis syndrome rather than the isolated atypical coarctation.

Severe aortic insufficiency is said to be the one of the important etiology of the reversed splitting.[29] Dickerson and Nelson[5] also listed this entity as one cause of the reversed splitting due to left ventricular volume load, but their illustration remained some equivocal points, because 1) some beats during expiratory

and inspiratory phases had the second heart sound of the same duration without appreciable splitting (Fig. 3,[5] the 2nd and 4th second heart sounds), 2) the murmur of aortic insufficiency is so faint (or not well inscribed) that the possibility of severe insufficiency is not likely, and 3) the electrocardiogram shown in their figure seems to have a pattern of myocardial infarction. On the other hand, aortic insufficiency usually seen in the aortitis syndrome is of mild degree, so that it can not be regarded as a main cause of reversed splitting. Without aortic insufficiency, reversed splitting was observed in 3 cases, which otherwise have similar clinical situation to the other cases with reversed splitting. By these reasons, it was not concluded that aortic insufficiency co-existed had the primary importance to the reversed splitting.

Recently, the role of myocardial competence on the behavior of the splitting of the second heart sound has been postulated by several authors. Wood[33] suggested that transient reversed splitting during the attack of angina pectoris would be due to the transient elevation of blood pressure. Describing 7 coronary patients with reversed splitting by auscultation, Yurchak and Gorlin[30] postulated that the ballooning of ischemic area, possible but undetected transient (left bunble branch) block, impaired ventricular relaxation and aortic valve closure, and early closure of the pulmonic valve due to elevated pulmonary artery pressure secondary to the left ventricular failure could be the contributing factors. Subsequent report[43] emphasized the role of shortened right ventricular ejection period, though it was not measured in their study. Dickerson and Nelson[5] emphasized that " unexplained " reversed splitting may be a valuable " bedside indicator " of left ventricular dysfunction. Similar opinion was proposed by some authors using phonocardiographic confirmation. Abbott and Whipple[26] are of the opinion that reversed splitting seen in the occasional cases of hypertension may be the reflection of compromised myocardium rather than the elevated aortic pressure *per se*. Using both phonocardiogram and mechanocardiogram, Holldack and his associates[31] made the daily follow-up study in 80 cases of acute myocardial infarction and found 9 cases with reversed splitting (2 cases showed complete left bundle branch block). They postulated that the common denominator of the hemodynamically induced reversed splitting could be the moderate insufficiency of left ventricular contraction with prolonged Q-IIA interval. At the same time, the shortening of Q-IIP, or at least constant Q-IIP, may also be contributing. Agnew et al.[32] recorded reversed splitting in 12 cases of ischemic heart disease, including one of "right" bundle branch block. They noted that frequent association of ventricular gallop and reversed splitting and suggested that reversed splitting is an indication of left ventricular dysfunction.

Though the present study did not reveal the direct evidence, several points,

which are in favor of myocardial incompetence in cases with reversed splitting, deserve emphasis. Firstly, as Agnew et al.[32] pointed out, the cases with reversed splitting frequently had gallop rhythm, particularly the ventricular gallop, which indicates the diastolic overloading of the left ventricle. In the absence of severe regurgitation of either aortic or mitral valve, this indicates the myocardial incompetence in most cases.[44] Secondly, abnormal QT prolongation was frequently observed in cases with reversed splitting. QT prolongation in the group without reversed splitting was not marked and did not accompany with the split second sound, whereas the splitting of usual sequence of the 2 components (IIA-IIP) was exclusively observed in cases with normal QT interval. This indicates that QT interval is the one of the important factor to stabilize the position of IIA in the cardiac cycle. QT prolongation in myocardial disease is a well-known fact,[45] and it is worthwhile to observe this phenomenon in aortitis syndrome (Takayasu's arteritis) without QRS widening, hypocalcemia, and other factors which contribute to the QT prolongation. Thirdly, the patho-anatomy of the heart in aortitis syndrome may be responsible for the myocardial incompetence. Previous report from our Department confirmed the presence of diffuse and marked myocardial fibrosis, which was particularly marked in the perivascular region.[7] Data of 72 autopsy cases reviewed[46] also showed the occasional presence of thickening of wall, narrowing or obstruction of the lumen, edematous thrombus of intima, and atheroma or thrombus formation in the coronary artery. Thus, all of the phonocardiographic, electrocardiographic, and possible patho-anatomic studies suggest that myocardial incompetence influences the occurrence of reversed splitting. Indeed, this postulate may be worth further study as a mechanism for the changes of the second heart sound observed in the present study.

References

1. Wolferth, C. C. and Margolies, A.: Am. Heart J. **10**: 425, 1935.
2. Gray, I. R.: Brit. Heart J. **18**: 21, 1956.
3. Ueda, H., Kaito, G., and Sakamoto, T.: Clinical Phonocardiography, Nanzando, Tokyo, p. 150, 1963 (in Japanese).
4. Leatham, A.: Acta cardiol. **19**: 395, 1964.
5. Dickerson, R. B. and Nelson, W. P.: Am. Heart J. **67**: 410, 1964.
6. Ueda, H. and Sakamoto, T.: Nippon-Rinsho **19**: 87, 1961 (in Japanese).
7. Yamada, H., Harumi, K., Ohta, A., Nomura, T., Okada, R., and Ishii, M.: Jap. Heart J. **2**: 538, 1961.
8. Ueda, H., Kaito, G., and Sakamoto, T.: *op. cit.*, p. 893.
9. Ueda, H., Sakamoto, T., Yamada, T., Uozumi, Z., Kobayashi, T., Kawai, N., Inoue, K., and Kaito, G.: Jap. Heart J. **7**: 3, 1966.
10. Sakamoto, T., Uozumi, Z., Katio, G., and Ueda, H.: Jap. Heart J. **7**: 154, 1966.
11. Ueda, H., Sakamoto, T., Takeda, T., Uozumi, Z., Yamada, T., Nakamura, H., and Tagawa,

H.: Jap. Heart J. **9**: 142, 1968.
12. Ueda, H., Katio, G., and Sakamoto, T.: *op. cit.*, p. 629.
13. Haber, E. and Leatham, A.: Brit. Heart J. **27**: 691, 1965.
14. March, H. W., Selzer, A., and Hultgren, H. N.: Circulation **23**: 582, 1961.
15. Zuberbuhler, J. R. and Bauersfeld, S. R.: Am. Heart J. **70**: 595, 1965.
16. Zuberbuhler, J. R., Bauersfeld, S. R., and Pontius, R. G.: Am. Heart J. **74**: 816, 1967.
17. Leatham, A.: Lancet **2**: 607, 1954.
18. Wood, P.: Am. J. Cardiol. **1**: 533, 1958.
19. Calo, A.: Jap. Heart J. **3**: 299, 1962.
20. Braunwald, E., Goldblatt, A., Aygen, M. M., Rockoff, S. D., and Morrow, A. G.: Circulation **27**: 426, 1963.
21. Braunwald, E., Morrow, A. G., Cornell, W. P., Aygen, M. M., and Hiblish, T. F.: Am. J. Med. **29**: 924, 1960.
22. Fishleder, B. L., Bermudez, F., and Friedland, Ch.: Arch. Instit. Cardiol. México **32**: 430, 1962.
23. Yoshimura, S., Sugai, J., and Sato, Y.: Phonocardiography. Igakushoin, Tokyo-Osaka, p. 62, 1962 (in Japanese).
24. Michel, D.: Angeborene Herzfehler. Auskultation·Phonokaridographie·Differentialdiagnose. Springer, Berlin·Göttingen·Heidelberg, p. 32, 1964.
25. Shah, P. M. and Slodki, S. J.: Circulation **29**: 551, 1964.
26. Abbott, J. A. and Whipple, G. H.: Dis. Chest **46**: 304, 1964.
27. Ravin, A.: Auscultation of the Heart. 3rd. ed., Year Book Medical Publishers, Chicago, p. 59, 1967.
28. Ueda, H., Sakamoto, T., Uozumi, Z., Inoue, K., Kawai, N., and Yamada, T.: Jap. Heart J. **7**: 204, 1966.
29. Fishleder, B. L.: Exploracion Cardiovascular y Fonomecanocardiografía Clinica. La Prensa Médica Mexicana, México, p. 160, 1966.
30. Yurchak, P. M. and Gorlin, R.: New Engl. J. Med. **269**: 741, 1963.
31. Holldack, K., Fuchs, G., Zapfe, H., and Mähler, L.: Z. Kreislaufforschg. **56**: 541, 1967.
32. Agnew, T., Bucher, H., McDonald, L., and Seymour, J.: Brit. Heart J. **29**: 775, 1967.
33. Wood, P.: Brit. med. J. **1**: 1779, 1961.
34. Ueda, H., Sakamoto, T., Uozumi, Z., Kawai, N., Yamada, T., Inoue, K., and Chang, S. Y.: Presented at the 44th Kanto-Koshinetsu-Hokuriku Regional Meeting of Jap. Circulat. Soc., May, 1967 (Abstr. Jap. Circulat. J. **31**: 1505, 1967 . . . in Japanese).
35. Boyle, J., III. and Little, R. C.: Am. Heart J. **68**: 91, 1964.
36. Furuta, S.: Jap. Circulat. J. **23**: 282, 1959 (in Japanese).
37. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease. 2nd ed., The Year Book Publishers, Chicago, p. 733, 1959.
38. Benchimol, A. and Dimond, E. G.: Am. J. Med. **28**: 347, 1960.
39. Ueda, H., Kaito, G., and Sakamoto, T.: *op. cit.*, p. 587.
40. Barlow, J. and Kincaid-Smith, P.: Brit. Heart J. **22**: 505, 1960.
41. Yamakawa, K., Ohta, H., Mishina, D., Saeki, H., and Machii, K.: Respiration & Circulation **3**: 573, 1955 (in Japanese).
42. Inada, K., Shimizu, H., Ishiai, S., Kobayashi, I., and Kawamoto, S.: Respiration & Circulation **9**: 15, 1961 (in Japanese).
43. Cohen, L. S., Elliott, W. C., Rolett, E. L., and Gorlin, R.: Circulation **31**: 409, 1965.
44. Harvey, W. P. and Segal, J. P.: Circulation **18**: 1017, 1958.
45. Lepeschkin, E.: Modern Electrocardiography. Vol. I. The P-Q-R-S-T-U Complex. Williams & Wilkins, Baltimore, p. 187 & 460, 1951.
46. Committee Report: Clinical and Pathological Studies of Aortitis Syndrome. Jap. Heart J. **9**: 76, 1968.

Pulmonary Regional Ventilation-Perfusion Relationships in Chronic Cardiopulmonary Disorders

II. Scintiscanning Method

Hideo Ueda, M.D., Hajime Morinari, M.D., Shuichi Hatano, M.D., Masahiro Iio, M.D., Masashi Mori, M.D., Shigeo Koike, M.D., *and* Makoto Murao*, M.D.

Summary

This is the study attempting to clarify quantitatively the regional disturbance of ventilation-perfusion relationships in pulmonary diseases. Measurements were made on 7 normal subjects, 16 cases with pulmonary parenchymal diseases and 4 cases with pulmonary vascular diseases. Perfusion and inhalation scintigrams were taken in sitting position and were divided into 9 horizontal zones in order to know relative values of regional pulmonary blood flow ($\dot{Q}$) and alveolar ventilation ($\dot{V}_A$). Cardiac output and minute alveolar ventilation were also obtained at the same time. Using these data, absolute values of regional $\dot{V}_A$, $\dot{Q}$ and $\dot{V}_A/\dot{Q}$ of 9 zones were analyzed from the base to the apex of both lungs.

In 7 normal subjects the average regional $\dot{V}_A/\dot{Q}$ ratio was 0.64 at the base and increasing 1.35 at the apex. In 20 patients the ratio ranged between 0 and 11.2, and even in the parts of parenchymal disorders the ratio was generally higher than normal since the decrease of regional perfusion was more remarkable than that of regional ventilation.

Discussions were made on the usefulness as well as limitations of this scintiscanning method in approaching ventilation-perfusion unevenness topographically and quantitatively.

Additional Indexing Words :

Pulmonary perfusion scintiscanning Inhalation scintiscanning Influence of body position Hypoxia Gas exchange Ultrasonic nebulizer

VENTILATION-PERFUSION unevenness is one of the causes of hypoxemia and the abnormality of which has been studied as a whole lung in various ways, but the topographical analysis of the unevenness has been difficult to study until the recent advances of radioisotope techniques. In the previous paper[1] we reported a study of regional ventilation-perfusion relationship using radioac-

From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo.

* Present address: The First Department of Internal Medicine, Hokkaido University, Sapporo.

Received for publication August 10, 1968.

tive rare gases. In this paper we will report the analysis of regional ventilation and perfusion using inhalation and perfusion scintiscanning method. The method, the results and the limitations of our study are presented.

Methods and Materials

Twenty-seven patients were studied. Seven of them were normal control having no evidence of cardiopulmonary diseases confirmed both by clinical and laboratory examinations including chest X-ray films. The other 20 cases had various pulmonary diseases, 16 with parenchymal diseases and 4 with pulmonary vascular diseases. All the 20 cases studied were listed in Table I with the diagnosis and the results of arterial blood gas analysis.

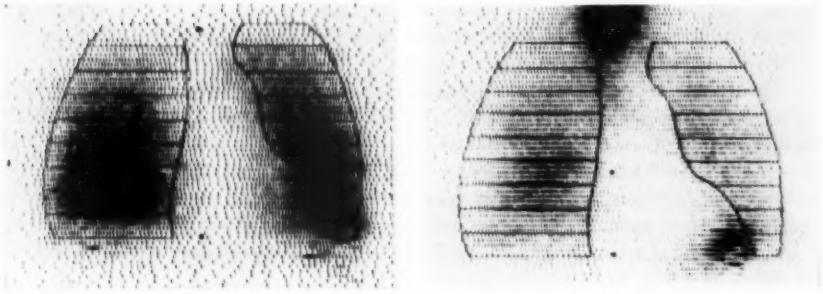
For the study of the regional ventilation, inhalation scintiscanning, which is similar to Alterbrunn's[2] and Taplin's[3] method, was tried using 1.5–2.0 mCi of Au^{198} colloid aerosol. Inhalation of the aerosol was assisted by the use of respirator which was set at the positive pressure of 8 cm.H_2O. The expired gas was collected in the bag and was released into the atmosphere after the decline of the radioactivity to avoid the contamination of the room. Regional perfusion study was done according to the reported methods[4),5)] with I^{131}-macroaggregated albumin (I^{131}-MAA)

Table I. Cases with Chronic Cardiopulmonary Disorders

No.	Name	Age	Sex	Diagnosis	PaO_2 mm.Hg
1	J. T.	78	M	Pulmonary cancer of the left lung	71.2
2	K. Y.	65	M	Pulmonary cancer of the left lung	62.6
3	E. S.	40	M	Multiple bronchogenic cysts of the left lung	61.9
4	K. A.	34	M	Multiple bronchogenic cysts of the left lung	
5	H. K.	51	F	Pulmonary cysts of the right lung	96.8
6	H. H.	57	M	Pulmonary cysts of the right lung	85.0
7	Y. M.	52	M	Vanishing lung	80.0
8	Y. S.	58	M	Chronic pulmonary emphysema	
9	S. T.	66	M	Chronic pulmonary emphysema	83.5
10	A. N.	70	F	Chronic pulmonary emphysema	55.3
11	S. Y.	67	M	Chronic pulmonary emphysema	82.7
12	F. A.	68	F	Chronic pulmonary emphysema	36.0
13	K. I.	69	M	Chronic pulmonary emphysema and pleuritis of the left side	69.0
14	S. M.	19	M	Kartagener's syndrome	76.9
15	T. T.	56	M	Postinfectious pulmonary atelectasis of the right lower lobe	86.3
16	M. A.	52	F	Pulmonic regurgitation with dilated pulmonary artery	69.2
17	N. U.	35	F	Pulmonary hypertension with tricuspid insufficiency	93.5
18	M. K.	36	M	Fibroplastic sarcoma of pulmonary artery	75.0
19	K. H.	28	F	Attenuated pulmonary artery of the right lung	
20	M. S.	16	F	Pseudotruncus arteriosus communis	

Table II. $\dot{V}_A$, $\dot{Q}$, $\dot{V}_A/\dot{Q}$ Ratio Abnormalities Seen in Parenchymal and Pulmonary Vascular Diseases

$\dot{V}_Ai/\dot{Q}i$	$\dot{V}_Ai$	$\dot{Q}i$	Pulmonary parenchymal disorders	Pulmonary vascular disorders
↑	↓	↓↓	9	3
~	↓	↓	6	1
↓	↓↓	↓	4	0



(a) (b)

Fig. 1. Pulmonary scintigrams of a normal subject sitting upright, (a) perfusion scintigram, (b) inhalation scintigram.

which was injected 100–200 μCi intravenously. The studies were done in the sitting position in all cases. Inhalation and perfusion scintiscannings were done with several days interval considering the effect of residual background. Shimazu SCC-30 scintiscanner ($3''\phi \times 2''$ crystal) was used, which has multichannel 37 holes focusing collimator with the focusing distance of 10 cm. The collimator was set anterior to the chest wall 10 cm. from the plane of the anterior axillary line and regional dot countings were recorded. The lower edge of the clavicle and the fifth intercostal space were chosen as the upper and lower border of the lung field and recorded on the scintigram. Later chest X-ray film was superimposed on the scintigram to divide the lung field into 9 equal zones from the apex to the base (Fig. 1). The dots were counted in the each zone and the background counts were substracted. The values were further corrected according to the thickness of the lung and the response curve of the collimator. Thus the relative regional ventilation and perfusion were obtained. In the normal subjects regional alveolar Po_2, Pco_2 and R.Q. were calculated using the O_2-CO_2 diagram of Rahn and Fenn.[6] Here total alveolar ventilation and ventilation-perfusion ratio were assumed 5 L./min. and 0.85 respectively. For the calculation, Po_2 and Pco_2 of the mixed venous blood were assumed 40 and 46 mm. Hg respectively. Diffusion gradient was not taken into consideration. In some of the patients with pulmonary diseases, cardiac output was measured by Fick's method during cardiac catheterization. To obtain the total alveolar ventilation, the calculation was done from the equation $\dot{V}_A = \dot{V}co_2/F_Aco_2$ for the cases who had the expired gas analysis, and for the rest the calculation was done from the values of

the tidal volume assuming anatomical dead space equal to the weight in pounds.[7] Thus the absolute values of zonal $\dot{V}_A$, $\dot{Q}$ and $\dot{V}_A/\dot{Q}$ ratio were calculated and the values were tabulated. The mathematical equations used for the calculations are as follows.

$$\frac{V_{Ai}}{Q_i} = \frac{a_i}{b_i} \times \frac{\text{a.v.}}{\text{c.o.}}$$

$$a_i = \frac{(d_{hi}-c)\times f_i}{\sum_{i=1}^{18}\{(d_{hi}-c)\times f_i\}}$$

$$b_i = \frac{(d_{pi}-c')\times f'_i}{\sum_{i=1}^{18}\{(d_{pi}-c')\times f'_i\}}$$

d_h : counts of inhalation scintigram
d_p : counts of perfusion scintigram
c, c' : counts of background
f, f' : correction factor for the thickness of pulmonary tissue
a.v. : alveolar ventilation of total lung
c.o. : cardiac output

Results

1. Regional ventilation and perfusion in normal subjects sitting upright

Seven normal subjects were studied. $\dot{V}_A$, $\dot{Q}$ and $\dot{V}_A/\dot{Q}$ values were tabulated in Fig. 2 and were mapped in Fig. 3. The amount of both ventilation

Right Lung

R	P_{CO_2} mm. Hg	P_{O_2}	$\dot{V}_{Ai}/\dot{Q}_i$	$\dot{Q}_i$ L./min.	$\dot{V}_{Ai}$
1.10	37	114	1.4	0.12	0.17
0.95	39	108	1.0	0.22	0.23
0.84	40	102	0.9	0.33	0.31
0.78	41	98	0.8	0.45	0.35
0.70	42	93	0.7	0.51	0.38
0.70	42	93	0.7	0.58	0.39
0.65	42	88	0.6	0.58	0.37
0.70	42	93	0.7	0.51	0.33
0.78	41	98	0.8	0.36	0.29
				3.66	2.81

total

Left Lung

$\dot{V}_{Ai}$ L./min.	$\dot{Q}_i$	$\dot{V}_{Ai}/\dot{Q}_i$	P_{O_2} mm. Hg.	P_{CO_2}	R
0.17	0.12	1.4	114	37	1.10
0.22	0.20	1.0	108	39	0.95
0.27	0.26	1.0	108	39	0.95
0.30	0.33	0.9	102	40	0.84
0.31	0.35	0.9	102	40	0.84
0.29	0.33	0.9	102	40	0.84
0.26	0.27	1.0	108	39	0.95
0.22	0.22	1.0	108	39	0.95
0.16	0.13	1.2	111	38	1.00
2.19	2.20				

Fig. 2. Topographical values of $\dot{V}_A$, $\dot{Q}$, $\dot{V}_A/\dot{Q}$ ratio, alveolar P_{O_2}, P_{CO_2} and R. Q. in the normal sitting upright.

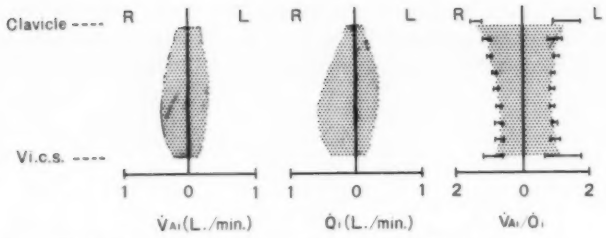


Fig. 3. Regional ventilation and perfusion in normal subjects.

and perfusion were smaller in the upper zone compared to those in the lower zone, while the values of $\dot{V}_A/\dot{Q}$ ratio ranged from 1.35 in the upper zone to 0.64 in the lower zone since the rate of decrease from the apex to the base was more prominent for perfusion than for ventilation. Using these values, alveolar-arterial gradient of Po_2 and Pco_2 were calculated and the results were 5 mm.Hg for oxygen and −0.3 mm.Hg for carbon dioxide which are within reasonable ranges compared to the values obtained by others.

2. Regional ventilation and perfusion in various pulmonary diseases

The values of regional $\dot{V}_A$, $\dot{Q}$ and $\dot{V}_A/\dot{Q}$ ratios were mapped in various lung diseases and are seen in Fig. 4.

Case 1 and case 2: bronchogenic carcinoma. In both cases bronchogram revealed compression of the left main stem bronchus and sign of local infiltrations. Both ventilation and perfusion were reduced in the involved side. Since the depression of perfusion was more marked, the calculated $\dot{V}_A/\dot{Q}$ ratio became high.

Case 3–7: cystic diseases of the lung. The relationship between ventilation and perfusion in this disorder was found to be various. In case 3, where the left lung was mainly involved, the decrease of both ventilation and perfusion was quite impressive with the predominant disturbance of the latter. Similar results were observed in other cases (case 4 and case 6) though the areas involved were different in each case. In case 5, where right middle and lower lobes were the site of major involvement, the decrease of ventilation and perfusion was found almost the same degree, thus maintaining normal $\dot{V}_A/\dot{Q}$ ratio. In case 7, there was a formation of an abscess in the cyst which was located in the left lung. The impairment of perfusion was found more predominant over the involved area, while in the right upper zone, where cystic lesions were also present, the impairment of ventilation was more predominant.

Case 8–13: chronic pulmonary emphysema. In some cases (case 8 and case 9) there was a marked regional decrease of ventilation, while in others (case 10–13) the changes were more or less diffuse without regional differences.

In the former group, there were formation of giant bullae in the right upper lobe which prevented the normal ventilation resulting in low $\dot{V}_A/\dot{Q}$ values. A compensatory increase of ventilation was also seen in the left lung of case 9.

Case 14: Kartagener's syndrome. In this case bronchiectatic changes were seen in both lower lobes, especially predominantly in the right side, and

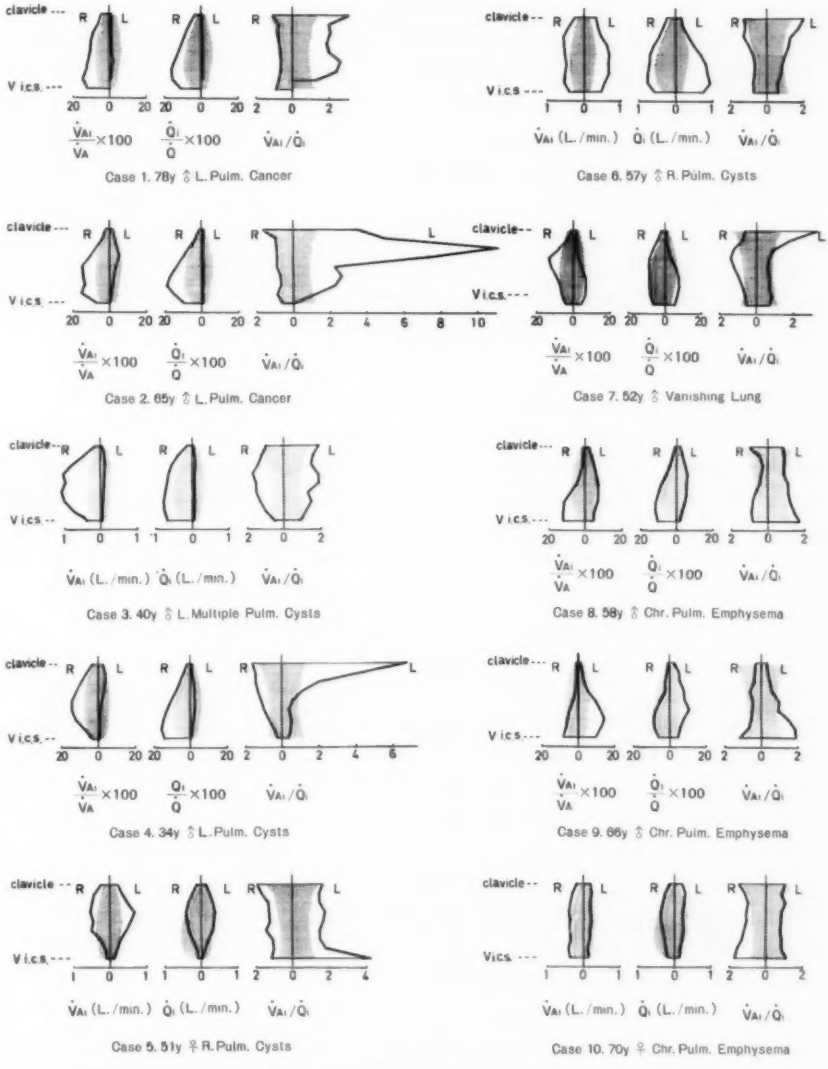
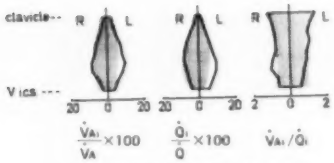

clavicle
V i.c.s.
R
L
$\frac{\dot{V}_{Ai}}{\dot{V}_A}\times100$
$\frac{\dot{Q}_i}{\dot{Q}}\times100$
$\dot{V}_{Ai}/\dot{Q}_i$
$\dot{V}_{Ai}$ (L./min.)
$\dot{Q}_i$ (L./min.)
Case 1. 78y ♂ L. Pulm. Cancer
Case 6. 57y ♂ R. Pulm. Cysts
Case 2. 65y ♂ L. Pulm. Cancer
Case 7. 52y ♂ Vanishing Lung
Case 3. 40y ♂ L. Multiple Pulm. Cysts
Case 8. 58y ♂ Chr. Pulm. Emphysema
Case 4. 34y ♂ L. Pulm. Cysts
Case 9. 66y ♂ Chr. Pulm. Emphysema
Case 5. 51y ♀ R. Pulm. Cysts
Case 10. 70y ♀ Chr. Pulm. Emphysema

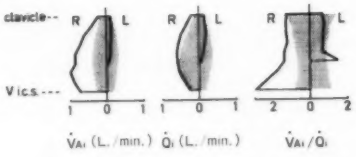
Fig. 4. Regional ventilation and perfusion in various pulmonary diseases.

there was a poor developement of the left upper lobe, producing an expansion and elevation of the left lower lobe. The study showed a decrease of ventilation and perfusion in the left upper zone (Fig. 4). The pattern was similar in the right lower zone but the decrease of perfusion was found to be more predominant.

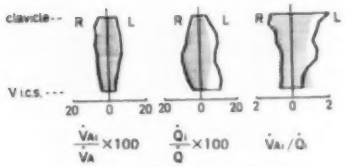
Case 15. In this case the scintigram did not reveal any significant abnor-



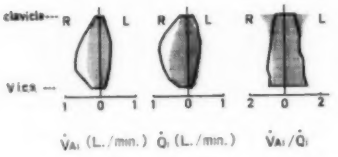
Case 11. 67y ♂ Chr. Pulm. Emphysema



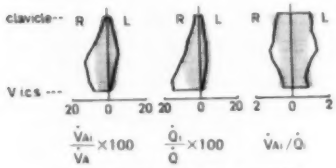
Case 16. 52y ♀ Compression of L. Main Br.



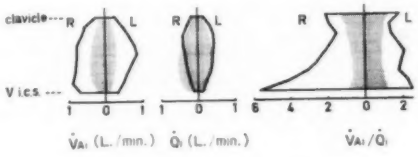
Case 12. 68y ♀ Chr. Pulm. Emphysema



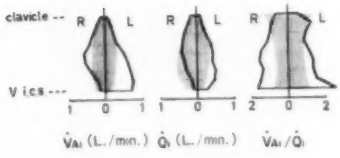
Case 17. 35y ♀ Susp. Pulm. Thrombosis



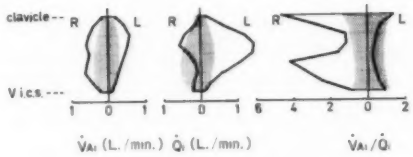
Case 13. 69y ♂ Chr. Pulm. Emphysema



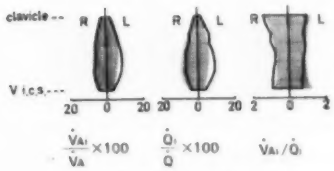
Case 18. 36y ♂ Fibroplastic Sarcoma of PA



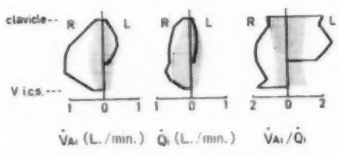
Case 14. 19y ♂ Kartagener's Synd.



Case 19. 28y ♀ Hypoplasia of R. PA



Case 15. 56y ♂ Atelectasis of R. Lower Lobe



Case 20. 18y ♀ Pseudotruncus Art. Communis

malities, though the patient had an atelectasis of right lower lobe after bronchopneumonia. Probably the abnormality was masked by the expanded right middle and upper lobe over the atelectatic area.

Case 16. In this case the scintigrams showed almost no ventilation and perfusion to the left lower zone which was thought to be due to the shift of the heart to the left. The patient had pulmonic regurgitation with the ectasia of pulmonary artery compressing left main stem of bronchus. There was also a pleural adhesion due to old pleuritic changes. Calculated $\dot{V}_A/\dot{Q}$ over the left zone was 0.69, indicating the more predominant ventilatory impairment. In the next 4 cases, pulmonary vessels are the sites of major involvement.

Case 17. This is the case of pulmonary hypertension probably caused by multiple pulmonary emboli. Both ventilation and perfusion were reduced almost the same degree.

Case 18. Pulmonary embolism was suspected clinically, but postmortem examination revealed fibroblastic sarcoma involving pulmonary artery. Prominent decrease of perfusion to the right lower zone was seen in the scintigram. Since there was no parallel decrease of ventilation $\dot{V}_A/\dot{Q}$ ratio became as high as 5.7.

Case 19. Poor development of right pulmonary artery was demonstrated by pulmonary arteriogram. Ventilation of the right lung was relatively normal but perfusion to the apex, middle and lower lobes were poor resulting in an unusual configuration in the figure of regional mapping of $\dot{V}_A/\dot{Q}$ ratios. Drop of $\dot{V}_A/\dot{Q}$ ratio in the left middle zone is probably explained by the compensatory shift of blood flow from the right lung to the left lung.

Case 20. Pseudotruncus arteriosus communis and hypoplasia of the left lung. Prominent decrease of perfusion to the hypoplastic lung was seen. Ventilation was also decreased but is a lesser degree.

We have divided the abnormal zones into 3 groups depending on the values of regional ventilation-perfusion ratio, that is high, normal, or low. When $\dot{V}_A/\dot{Q}$ ratio of a certain zone is within one standard deviation from the mean of the $\dot{V}_A/\dot{Q}$ ratios of this zone in the normal control, we have accepted the $\dot{V}_A/\dot{Q}$ ratio of this zone as normal. Out of 19 abnormal zones in the 16 cases of parenchymal lung diseases, $\dot{V}_A/\dot{Q}$ was higher than normal in 9, normal in 6 and lower in 4. In 4 cases of pulmonary vascular diseases high $\dot{V}_A/\dot{Q}$ ratio was found in 3 cases and normal in 1. None had the values lower than normal (Table II).

Next we have tried to see the relationship between the arterial Po_2 and the variance of $\dot{V}_A/\dot{Q}$ ratio. The variance was calculated as the deviation of the $\dot{V}_A/\dot{Q}$ ratios of the each zone from the mean of the corresponding zones in the normal expressed in logarithmic scale. The formula used for the cal-

culation is as follows.

$$\text{The variance of } \dot{V}_A/\dot{Q} \text{ ratio} = \sqrt{\frac{\sum^{18}\left[\log\left(\frac{\sum^{18} V_{Ai}}{\sum^{18} Q_i}\right)-\log\left(\frac{V_{Ai}}{Q_i}\right)\right]^2}{18}}$$

In Fig. 5 indices of $\dot{V}_A/\dot{Q}$ variance were plotted in the abscissa and the values of arterial Po_2 in the ordinate to see the correlation between the two. The plottings show the presence of a negative correlation; in other words, the higher the variance, the lower the arterial Po_2.

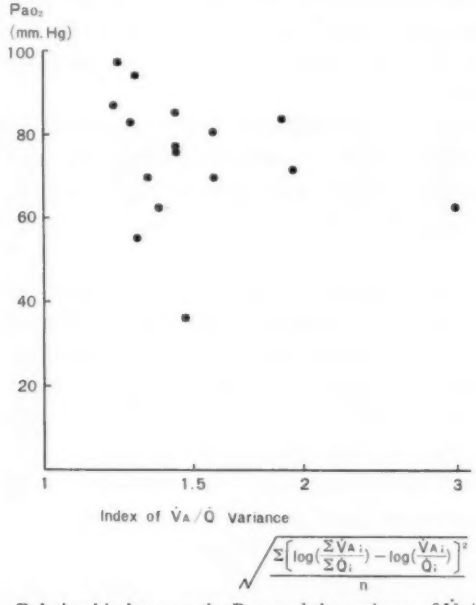


Fig. 5. Relationship between the Pao_2 and the variance of $\dot{V}_A/\dot{Q}$ ratio.

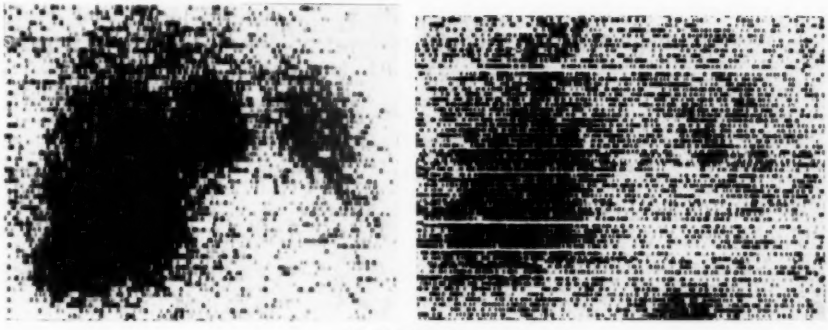
Discussion

Since the report of the Björkman in 1934[8] there have been many studies which states the decrease of both ventilation and perfusion in the upper part compared to the lower part of the lung and inequal ventilation-perfusion ratios between the upper and lower segments.[9] Various methods have been used for the study. In our study both inhalation scintiscanning and perfusion scintiscanning were applied using Au^{198} colloid aerosol in the former and I^{131}-MAA in the latter. The entire lung fields were divided into 9 horizontal belts. The $\dot{V}_A/\dot{Q}$ ratio ranged between 1.35 and 0.64, the values being higher in the upper zone.

The differences of $\dot{V}_A/\dot{Q}$ ratio between the upper and lower zones are smaller here compared to those reported by the others.[10)–13)] This difference can be related to the methodological differences. In our method, I^{131}-MAA or Au^{198} colloid aerosol was given in the sitting position, while the counting was done in the supine position. It is quite possible that the zone of our scintigram does not necessarily corresponds to the same zone in the chest film taken upright. For instance the area under clavicle in the scintigram may correspond actually to the zone below the clavicle in the chest film. Also in the supine position the amount of pulmonary tissue which lies under the zone of the fifth intercostal space will become decreased due to the elevation of the diaphragm. All these geometrical relationships may influence the values of $\dot{V}_A/\dot{Q}$ ratios in our calculation.

In our method, the difference in regional ventilation or perfusion can be picked up more precisely compared to the method which uses CO_2[15] or radioac-

K. A. 34 yrs. ♂
l. multiple pulmonary cysts



Inhalation Scan

with pressure-cycled respirator with ultrasonic nebulizer

Fig. 6. Comparison of the 2 inhalation scintiscanning methods.

tive rare gases. But there is a methodological weakness in that the measurements of ventilation and perfusion should be done separately; in other words, there was a time lag between the 2 measurements. The next argument is the validity of our measurement of regional ventilation. For the measurement of regional ventilation, Au^{198} colloid aerosol was inhaled under low positive pressure breathing which may disturb the pattern of spontaneous breathing. Later, we have tried the use of ultrasonic nebulizer for inhalation scintiscanning, since we can eliminate the influence of positive pressure breathing in this method. Fig. 6 illustrates the difference in the inhalation scintiscanning in both methods done in a patient with multiple pulmonary cysts. After several more studies, it was found that there is not a significant difference in the inhalation scintigram obtained in both methods.

There have been few studies done on the actual distribution of $\dot{V}_A/\dot{Q}$ ratios in the patients of pulmonary diseases using such a method. It has been said that in cystic lung disease ventilation and perfusion decrease in parallel,[14] while in chronic bronchitis or emphysema the change in $\dot{V}_A/\dot{Q}$ ratio is variable[15] but generally tends to decrease more or less.[16),17] In our study there were many cases where the $\dot{V}_A/\dot{Q}$ ratios were normal or even higher than normal over the diseased area, though the basic diseases in our study were not the same as those reported by others. Our results are in agreement with our previous study using radioactive rare gases.[1]

Since the unevenness of ventilation-perfusion ratio is one of the cause of hypoxemia, we have calculated the variance of $\dot{V}_A/\dot{Q}$ ratios in each case and plotted against the values of arterial oxygen tension to see the correlation between the two. There was a negative correlation though the correlation was rather poor, which is rather expected since the variance of $\dot{V}_A/\dot{Q}$ ratios is not the only cause of hypoxemia and our method does not necessarily reflect the $\dot{V}_A/\dot{Q}$ abnormality at the alveolar level.

For the actual performance of the measurement, it was hard to correct the counting according to the thickness of the lung and locate the exact position in the apex. Also at the base the respiratory motion of the diaphragm interferes with the regional geometry. For these reasons, we have discarded the measurement of the zones above clavicle and below sixth rib. It is possible that the difference in $\dot{V}_A/\dot{Q}$ ratios becomes higher between the apex and the base if we included these two zones for the study. The lesion located just below the chest wall and the one located posteriorly close to the back were not treated equally in our study due to the response of the collimator used, and the regional differences in relation to the anteroposterior axis cannot be measured in our study, though these two drawbacks are inevitable in the other studies using CO_2[15] or radioactive rare gases at present.

The measurements of cardiac output and alveolar ventilation were done separately and the difference of cardiac output in relation to the change in position was not taken into consideration in our study. The overcoming of these methodological limitations and the correction of the possible errors remain for our future effort.

References

1. Ueda, H., Hatano, S., Iio, M., Kaihara, S., Morinari, H., Koike, S., and Murao, M.: Jap. Heart J. **8**: 559, 1967.
2. Altenbrunn, H. J.: Nuclear Med. **4**: 221, 1964.
3. Taplin, G. V., Poe, N. D., and Greenberg, A.: J. Nucl. Med. **6**: 348, 1965.
4. Wagner, H. N., Sabiston, D. C., Iio, M., McAfee, J. G., Meyer, J. K., and Langan, K. L.: J. A. M. A. **187**: 601, 1964.
5. Ueda, H., Iio, M., and Kaihara, S.: Jap. Heart J. **5**: 431, 1964.
6. Rahn, H. and Fenn, W. O.: A graphical analysis of the respiratory gas exchange. The O_2-CO_2 diagram. Am. Physiol. Soc. Washigton D. C., 1955.
7. Radford, E. P., Ferris, B. J., and Kriete, B. C.: New Engl. J. Med. **251**: 877, 1954.
8. Björkman, S.: Acta Med. Scand., Suppl. **56**: 1, 1934.
9. Bates, D. V.: Measurement of regional ventilation and blood flow distribution. in Handbook of Physiology, Section 3, Volume 2. Am. Physiol Soc. Washington D. C. pp. 1425–1436, 1964.
10. West, J. B.: J. Appl. Physiol. **1**: 893, 1962.
11. Knipping, H. W., Bolt, W., Venrath, H., Valentin, H., Ludes, H., and Endler, P.: Dtsch. Med. Wschr. **80**: 1146, 1955.
12. Bryan, A. C., Bentivoglio, L. G., Beerel, F., MacLeish, H., Zidulka, A., and Bates, D. V.: J. Appl. Physiol. **19**: 395, 1964.
13. Dollery, C. T. and Gillam, P. M. S.: Thorax **18**: 316, 1963.
14. Dollery, C. T. and Hugh-Jones, P.: Brit. Med. Bull. **19**: 59, 1963.
15. Bentivoglio, L. G.: Dis. Chest **48**: 502, 1965.
16. Lenfant, C. and Pace, W. R., Jr.: J. Clin. Invest. **44**: 1566, 1965.
17. Riley, R. L. and Cournand, A.: J. Appl. Physiol. **1**: 825, 1949.

Nervous Control of the Renal Tubular Function

Jugoro Takeuchi, M.D., Nobuo Ohya, M.D., Shuichiro Sakai, M.D.,
Haruo Nakamura, M.D., Tetsuo Nohara, M.D.,
Kunihiko Hirasawa, M.D., *and* Akira Shinoda, M.D.

Summary

The role of the renal nerves in renal tubular function—which is still a controversial subject—was studied by observing the changes in renal nerve activity and urine formation before, during and after the left stellate ganglion stimulation. The experiments were performed on 7 dogs anesthetized with a combination of morphine and α-chloralose. The activity of one of the renal nerves was picked up by a platinum bipolar electrode and recorded. During the left stellate ganglion stimulation, the rate of discharge of renal nerve activity decreased in the number of bursts and, at the same time, increases in urine volume and excretion of sodium, potassium and solutes were observed, while the urinary concentrations of sodium, potassium and osmolality decreased. These alterations produced by stellate ganglion stimulation were characterized by a rapid onset and, with cessation of stimulation, a rapid disappearance. There was observed complete recovery after the stimulation. On the other hand, the estimation of glomerular filtration rate revealed no significant changes through each experimental period.

The mechanisms of stellate ganglion stimulation diuresis were discussed and it was assumed that there was nervous control operating on renal tubular function, especially in the proximal tubules.

Additional Indexing Words :

Renal nerve activity Stellate ganglion stimulation diuresis Bipolar electrode Sodium transport Sodium reabsorption

IT has been a well known fact that the activation of renal efferent nerves exerts a vasoconstrictive effect on renal vessels, especially under stress. However, it remains to be explored whether renal tubular cells have nerve supply and how renal efferent nerves affect tubular function. Many studies on the role of renal nerves in renal function have been performed by means of sectioning or electrical stimulation of the renal or splanchnic nerves. Another method of this study is the recording of the action potential of the renal nerve, in which the renal innervation from brain stem is thought to remain in a more

From the First Department of Internal Medicine, School of Medicine, University of Kanazawa, Kanazawa.

Received for publication July 29, 1968.

physiological state than in the former methods. Several authors[1)–5)] have observed the renal nerve discharge under various conditions, mainly in order to study the relationship between renal nerve activity and renal circulation.

In 1964, Gilmore[6)] observed that the left stellate ganglion stimulation caused acute diuresis and postulated this phenomenon as an effect of withdrawal of renal sympathetic vasoconstrictive nerve discharge. But, one should consider the possibility that the renal sympathetic nerve may have a direct effect on renal tubular function.

In the present study, experiments were carried out to investigate nervous control in the renal tubular function by observing the changes in renal nerve activity, urine volume and urinary constituents before, during and after acute hypertension produced by the electrical stimulation of the left stellate ganglion.

Materials and Methods

Twenty-five experiments were performed in 7 mongrel dogs weighing 9 to 13 Kg. They were anesthetized with a combination of morphine hydrochloride (6 mg./Kg., intramuscularly) and α-chloralose (100 mg./Kg., intravenously), with supplementation of α-chloralose as required. The trachea was intubated for positive pressure breathing and the required vessels were exposed. Urine was collected by free drainage into graduate cylinders through a polyethylene catheter inserted into the ureter and the femoral arterial blood pressure was recorded with a strain gauge electric manometer (Nihon Kohden MP-4).

Following the collection of preliminary samples of blood and urine, a priming injection of 660 mg. of thiosulfate was given intravenously and then sustaining infusion of 50 mg./ml. of thiosulfate in normal saline was started at a constant rate of 0.5 ml./min.

Stimulation of the stellate ganglion: After opening the chest by cutting off the posterior angle of the left second rib, the left stellate ganglion was isolated and all rami except the cardiac sympathetic outflow were sectioned. The stellate ganglion was then placed on a shielded bipolar silver electrode connected to an electric stimulator (Nihon Kohden MSE-3). The stimulus was a series of repetitive pulses with a duration of 1 msec., a frequency of 10 cps. and an intensity varying 4 to 10 volts.

Recording renal nerve activity: The renal nerve employed was separated from the surrounding tissues in the left renal hilus and was not sectioned. The other nerves remained intact. The action potentials, picked up by a platinum bipolar electrode which was placed around the isolated nerve, were amplified, displayed on a cathode ray oscilloscope (Nihon Kohden VC-7), and also recorded on a multi-channel ink-writing recorder (Nihon Kohden RM-150). The arterial blood pressure was also recorded. In some experiments, an integrator was used for evaluating the changes in action potential. At the end of the experiments, it was ascertained that the employed nerve ran into the renal parenchym.

Chemical procedures: After a 90 to 120 min. equilibrium period following all operative procedures, urine samples were collected every 10 min. and blood

samples were drawn at the midpoints of urine collection periods from the antecubital vein. When experimental intervention was carried out, the urine for the first 5 min. or the first 2 to 3 ml. of urine collected were discarded. The renal clearance of thiosulfate was measured to evaluate glomerular filtration rate. Serum and urine thiosulfate were determined after the method of Brun.[7] Serum and urine were analyzed for sodium and potassium concentration using a Coleman flame spectrophotometer, for osmolality by Fiske Model G-62.

Results

Spontaneous discharges of the renal nerve activity were regularly recorded with the amplitude of 10 to 100 mV. They were considered efferent nerve activities since the form of discharge remained unchanged after cutting the nerve distal to the electrode (Fig. 1). The impulses occurred in bursts in synchronization with heart beat, as described in the previous reports on the renal nerve of dogs[5] and cats.[1] The impulses were not influenced by respiration in our experimental conditions. However, along with getting into terminal stage, the discharges became frequent to continuous (Fig. 1). The above mentioned recording was excluded from the results of the present study.

The results of stellate ganglion stimulation were as follows: stellate ganglion stimulation resulted in an elevation of mean arterial pressure, a marked widening of pulse pressure and, in most experiments, a decrease in

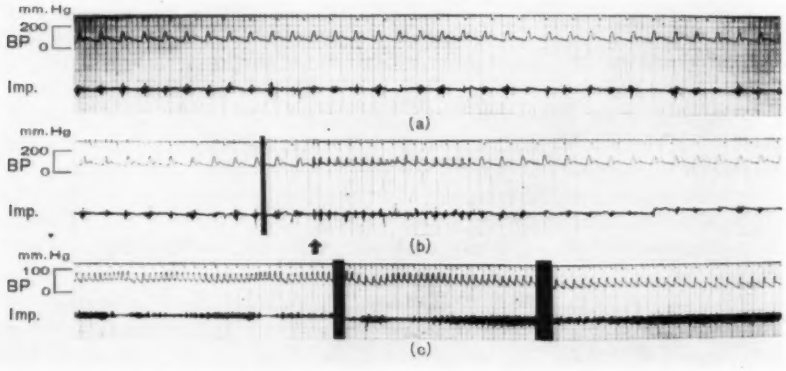


Fig. 1. Renal nerve activity.
(a) Spontaneous discharge. Note that impulses occur in bursts in synchronization with heart beats.
(b) Cutting the nerve distal to the electrode (↑).
(c) Discharges become frequent to continuous, along with getting into terminal stage.
BP: femoral arterial blood pressure. Imp.: impulse of the renal nerve. (Time: 1 division represents 1 sec.)

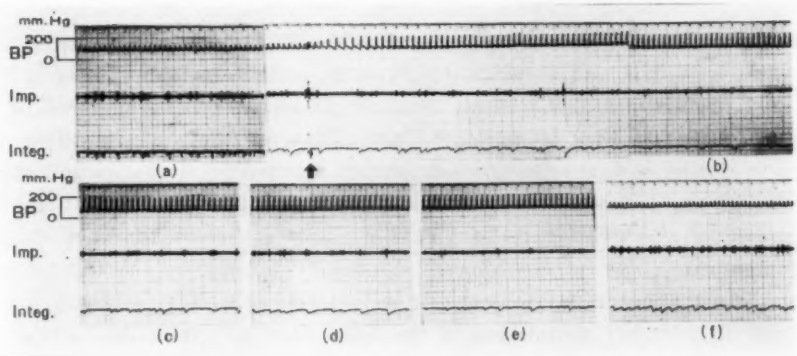


Fig. 2. The change in renal nerve activity following the left stellate ganglion stimulation.

(a) Before stimulation. (↑) Beginning of the stimulation

(b)-(e) During stimulation: 3 min. (b), 5 min. (c), 7 min. (d), 9 min. (e), after the beginning of stimulation

(f) At end of stimulation

Integ.: integration of the bursts

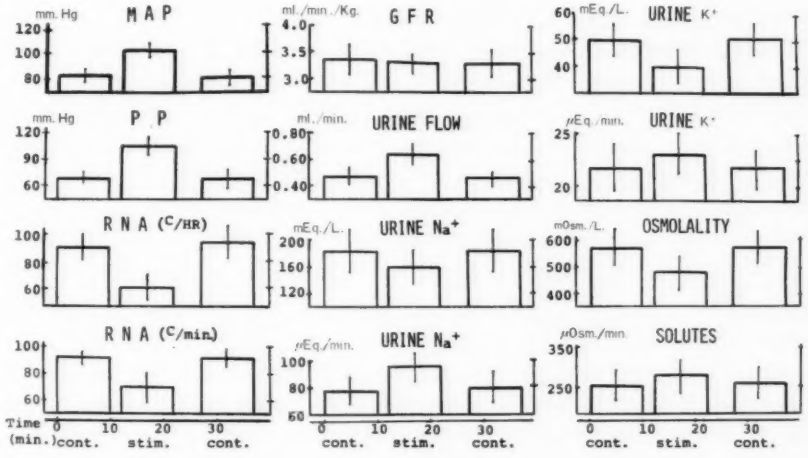


Fig. 3. Experiment illustrating the effect of stellate ganglion stimulation on hemodynamics, renal nerve activity, GFR and urinary constituents. MAP: mean arterial pressure, PP: pulse pressure, RNA: renal nerve activity, GFR: measured by thiosulfate clearance, Osmolality: total urinary solute concentration, Solutes: total urinary solute excretion.

heart rate. The effects of stellate ganglion stimulation on the discharging rate of the renal nerve were shown in Fig. 2. The discharging rate was expressed in both of C/HR and C/min.; C/HR is the averaged counts of the bursts during 100 heart beats, C/min. is the averaged counts of the bursts in a min. in each 10 min. observing period. The C/HR and C/min. decreased significantly during stellate ganglion stimulation ($p<0.01$), as shown in Fig. 3. Although the bursts inclined to occur in synchronization with heart beat, the decrease of the C/HR proved that the discharge *per se* decreased during stimulation.

The changes in urine formation in response to stimulation were shown in Fig. 3. During stimulation of the left stellate ganglion, the urine flow (0.64 ± 0.08 ml./min.) increased in all experiments as compared to the flow before and after stimulation (0.47 ± 0.06 and 0.47 ± 0.05 ml./min., respectively). Sodium and potassium concentration in the serum measured in 2 dogs remained constant in 1 experimental period for 40 min. In all experiments, except those in 1 dog in which urinary sodium concentration showed a slight increase, urinary concentrations of sodium and potassium declined during stimulation. The changes were statistically significant in 25 experiments ($p<0.01$). Urinary excretion of sodium and potassium increased significantly ($p<0.01$) with less change in potassium excretion. The urinary concentration of total solutes decreased ($p<0.01$) in 25 experiments.

It was noted that the changes were characterized by a rapid onset starting

Table I. Mean Values of Data Measured in This Study

		Control	Stimulation	Control
Heart Rate	(per min.)	100±12	90±10	105±15
MAP	(mm.Hg)	83±5	102±6	81±15
Pulse Pressure	(mm.Hg)	70±7	115±11	69±7
Urine Volume	(ml./min.)	0.47±0.06	0.64±0.08	0.46±0.05
GFR	(ml./min./Kg.)	3.36±0.29	3.33±0.25	3.30±0.25
	(C/HR)	92±5	70±11	91±6
RNA	(C/min.)	89±10	60±10	94±13
U_{Na^+}	(mEq./L.)	182±33	162±26	185±31
U_{K^+}	(mEq./L.)	50±6	40±7	51±6
Osmolality	(mOsm./L.)	560±63	480±67	576±60
U_{Na^+}	(μEq./min.)	78±11	96±12	79±12
U_{K^+}	(μEq./min.)	22±3	23±2	22±2
Solutes	(μOsm./min.)	255±39	285±36	260±39

MAP: mean arterial blood pressure, GFR: thiosulfate clearance,
RNA: renal nerve activity, C/HR and C/min.: see in the text, U: urine,
Osmolality: total urinary solute concentration, Solutes: total urinary solute excretion.

in $\frac{1}{2}$ to 1 min. from the beginning of stimulation and by a rapid disappearance within, at most, 5 min. from the cessation of stimulation. The values measured before and after stimulation were nearly equal.

The estimation of glomerular filtration rate revealed no significant changes through each experimental procedure ($0.2<p<0.5$) as shown in Fig. 3. In the present study, the thiosulfate concentration in the serum ranged from 14.5 to 61.9 mg./100 ml.

The mean values of the above data are shown in Table I.

Discussion

The results of the present experiments revealed increases in urine flow and in excretion of sodium, potassium and total solutes ; decreases in urinary concentration of these solutes during stellate ganglion stimulation, without any significant change in glomerular filtration rate. These results are similar to that of Gilmore's observation. Among humoral or neural factors as basic mechanisms of the diuresis, Gilmore[6] claimed the preponderance of neural reflex *via* baroreceptors to vasoconstrictive renal nerve.

In this report, the discrepancy between the change in glomerular filtration rate and the change in the rate of urine formation could be analysed considering the effects on renal function of the changes in systemic hemodynamics, humoral factor and renal nerve activity produced by stellate ganglion stimulation.

Changes in systemic hemodynamics : It has been generally accepted that the changes in renal arterial pressure and renal arterial pulse pressure within physiological range have little influence on renal blood flow and filtration rate.[8)–10)] The question raised is whether systemic hemodynamic changes produced by stellate ganglion stimulation are enough to influence urinary excretion directly. There have been many reports concerning the relationship between urinary excretion and renal hemodynamics. For example, Gesell[11] believed, from his experiments on dogs, that the reduction in pulse pressure caused diminution in urine flow and chloride excretion. Selkurt[12] reported that the level of the mean arterial pressure had a dominant role in the electrolytes and water handling ; that is, decreases and increases in the excretion of electrolytes and water were paralleled with the direction of change of the mean pressure. He concluded that renal interstitial pressure might influence renal tubular function. Thurau and Deetjen[13] reported that an increase in urine flow and a decrease in urinary osmotic pressure followed an increase in the pressure at which the blood perfused the kidney (*Druckdiurese*), and attributed the cause of this phenomenon to an increase in medullary blood flow, while total renal blood flow and, presumably, cortical blood flow remained relatively

constant in this circumstance.

In spite of these evidences, the hemodynamic changes as presented in our experiments do not appear to play a role on the diuresis in response to stellate ganglion stimulation according to the following facts: (a) in Gesell's report,[11] the time lapse between the change of pulse pressure and the onset of the change in urinary excretion was not constant and was longer than that observed in the present experiments ; in Selkurt's experiment,[12] the reduction of pulse pressure had no effect on renal function within a wide range of mean arterial pressure ; (b) according to Gottschalk's report,[14] the change in renal arterial mean pressure through 40 to 140 mm.Hg did not affect renal interstitial pressure ; (c) the experimental condition in the present report can not be compared with that of *Druckdiurese*[13] which was observed in the denervated kidney and 10 min. after an elevation of perfusion pressure ; (d) diuresis induced by stellate ganglion stimulation was characterized by a rapid onset, at the least $\frac{1}{2}$ min. and a rapid disappearance, within 5 min. after cessation of stimulation ; and (e) Gilmore reported that the diuresis induced by stellate ganglion stimulation decreased significantly subsequent to vagotomy, whereas changes in mean arterial pressure before and after vagotomy did not show a significant difference in response to stimulation.

Humoral factors : The next question is whether the stellate ganglion stimulation may be accompanied by changes in the secretion of ADH and aldosterone which affect renal tubular function. Although the elevation of the left atrial,[11)–17] the right atrial and the caval venous pressure[18] has been conceived to result in a decrease of ADH secretion and an increase of urinary excretion of aldosterone, respectively, it is known that the stellate ganglion stimulation lowers the atrial pressure.[6),19] The changes in urine flow and urinary constituents during stellate ganglion stimulation cannot be explained by the alteration of aldosterone secretion. Moreover, these humoral factors do not appear to cause the stellate ganglion stimulation diuresis characterized by rapid respondence, because the changes in urinary excretion of electrolytes due to these two hormones showed a slow onset and a relatively gradual disappearance.[15),18]

Renal nerve activity : From the previous discussion, it is strongly suggested that the stellate ganglion stimulation diuresis is associated with changes in renal nerve discharges. The acutely produced diuresis in the present experiments was characterized by its rapid respondence and each measurement shortly after stimulation was close to that before stimulation. In addition, renal nerve discharges decreased significantly during the stimulation. These facts are sufficient to support the hypothesis that a decrease in renal nerve discharge causes increases in urinary excretion of solutes and urine flow, decreases in concentration of urinary solutes which look like water diuresis except in rapid

respondence. An inference is drawn that an influence on change in renal nerve activity might be through renal tubular function, rather than glomerular filtration rates, since glomerular filtration rate before, during and after stimulation showed no significant changes in the present experiments. If so, how does the renal nerve act on the renal tubular function? Although the mechanism of dilution of the urine has been less adequately described, the following mechanisms might operate in the present experimental procedures: 1) depression in reabsorption of sodium in the proximal tubule, 2) inadequacy of sodium transport in the ascending limb of Henle's loop, 3) change in blood flow through the vasa recta, 4) depression in distal tubular reabsorption of sodium.

We shall first assume that a decrease in renal nerve activity causes a decrease in sodium reabsorption in the proximal tubule. Under this condition, total water and sodium flowing through the tubule distal to Henle's loop are supposed to increase and this results in an increase in sodium excretion and a decline in the sodium concentration in the urine. Since a major fraction of filtered potassium is reabsorbed in the proximal tubule and the most of potassium in the urine is presumably excreted by cation exchange of sodium for potassium in the distal tubule,[20),21)] potassium excretion may increase under the above assumed condition. The changes of urinary constituents in the present experiments are consistent with this assumption. It has been known that a depression in proximal tubular sodium reabsorption occurs in the natriuresis after a large dose of isotonic saline or a hypertonic saline load,[22)] but it remains to be resolved whether the identical mechanism operates in stellate ganglion stimulation diuresis.

A similar urine may be excreted following either interference of sodium transport in the ascending limb of Henle's loop or a change in blood flow in the vasa recta, through the depression of the medullary osmotic gradient. However, both of these mechanisms could not be supposed to operate when such rapid changes in urinary constituents are observed as in the present experiments.

Depression of the sodium reabsorption in the distal tubule may result in an increase in sodium excretion and a decrease in potassium excretion, if H^+ should not be exchanged for Na^+ than K^+ in the distal tubule.

By electron-microscopy, Hiraba[23)] examined renal tubular cells after cutting the renal nerves, and pointed out that the proximal tubular cells began to degenerate in 2 hours after denervation but that the other tubular portions distal to Henle's loop revealed no changes in longer periods. These results are reasonably appreciated from the facts that microscopic observations[24),25)] showed rich nerve supplies in the proximal tubular region and sparse supplies in the distal portions.

As discussed above, an assumption that the nervous control operates on renal tubular function especially in proximal tubules, is compatible with the morphological findings, although it is not denied that the changes in urine flow and urinary constituents during acute hypertension might be secondary to the minimal change in glomerular filtration rate undetectable by the present method.

References

1. Engelhorn, R.: Arch. Exp. Path. Pharmakol. **231**: 219, 1957.
2. Dieter, E.: Pflüger Arch. Ges. Physiol. **270**: 215, 1960.
3. McCubbin, J. W. and Page, I. H.: Circulat. Res. **6**: 816, 1958.
4. Yamakawa, J. and Ishiko, T.: J. Physiol. Soc. Japan **24**: 537, 1962 (in Japanese).
5. Takeuchi, J., Iino, S., Hanada, S., Sakai, S., Ohya, N., and Kitamura, K.: Jap. Heart J. **6**: 543, 1965.
6. Gilmore, J. P.: Circulat. Res. **14**: 301, 1964.
7. Brun, C. J.: J. Lab. Clin. Med. **35**: 152, 1950.
8. Selkurt, E. E., Hall P. W., and Sepencer, M. P.: Am. J. Physiol. **159**: 369, 1949.
9. Pitts, R. F. and Duggan, J. J.: J. Clin. Invest. **29**: 372, 1950.
10. Forster, R. P. and Meas, J. P.: Am. J. Physiol. **150**: 534, 1947.
11. Gesell, R. A.: Am. J. Physiol. **32**: 70, 1913.
12. Selkurt, E. E.: Circulation **4**: 541, 1951.
13. Thurau, K. and Deetjen, P.: Pflüger Arch. **274**: 567, 1962.
14. Gottschalk, C. W.: Am. J. Physiol. **163**: 716, 1950.
15. Henry, J. P., Gauer, O. H., and Reeves, J. L.: Circulat. Res. **4**: 85, 1956.
16. Gauer, O. H., Henry, J. P., and Sieker, H. O.: Prog. Cardiovas. Dis. **4**: 1, 1961.
17. Ledsome, J. R., Linden, R. J., and O.Connor, W. J.: J. Physiol. **159**: 87, 1961.
18. Davis, J. O., Kliman, B., Yandopoulos, N. A., and Peterson, R. E.: J. Clin. Invest. **37**: 1783, 1958.
19. Anzola, J. and Rushmer, R. F.: Circulat. Res. **4**: 302, 1956.
20. Watson, J. F.: J. Clin. Invest. **45**: 1341, 1966.
21. Davidson, D. G., Levinsky, N. G., and Berliner, R. W.: Am. J. Physiol. **37**: 548, 1958.
22. Rector, F. C., Gieson, G. U., Kill, F., and Seldin, D. W.: J. Clin. Invest. **43**: 341, 1964.
23. Hiraba, K.: Jap. J. Nephrol. **2**: 121, 1960 (in Japanese).
24. de Muylder, C. G.: The " Neurility " of the Kidney, Oxford, Blackwell, p. 24, 1952.
25. Mitchell, G. A. G.: Acta anat., Basel 13, 1951.

Experimental Arteritis Produced Immunologically in Rabbits

Hideo Ueda, M.D., Yoshimi Saito, M.D., Shigenori Morooka, M.D., Iwao Ito, M.D., Hisomu Yamaguchi, M.D., *and* Masaya Sugiura, M.D.

Summary

Pathological changes in the aorta and its major branches, which were similar, at least in part, to those seen in patients with aortitis syndrome, could be produced in rabbits by long-term administration of the isologous aortic extracts or the patients' sera containing anti-aorta antibodies of a high titer. The occurrence of vascular changes was preceded by a rise in the titer of the circulating complement fixing antibodies against the isologous aorta, suggesting that the vascular lesions are the product of a specific antigen-antibody reaction.

The results of the present study may support the authors' opinion that a certain immune mechanism participates in the development of arterial lesions in patients with aortitis syndrome.

Additional Indexing Words :

Aortitis syndrome Takayasu's arteritis Anti-aorta antibody Complement fixation test Eosinophilic body Anitschkow myocyte

THE etiology of aortitis syndrome (Takayasu's arteritis) remains unknown at present. However, participation of a certain immune process in its origin has been suggested by several laboratory data such as an accelerated erythrocyte sedimentation rate, positive C-reactive protein and increased serum α_2- and γ-globulin concentrations, which are frequently found in patients with aortitis syndrome, as well as by therapeutic effects of steroid hormones. In the previous investigations,[1] the authors detected anti-aorta antibodies in the sera of patients with aortitis syndrome by means of the complement fixation test and the direct fluorescent antibody technique.

The present study has been designed in an attempt to know whether experimental aortitis or arteritis might be produced in animals by immunological procedures.

From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo.

Received for publication July 30, 1968.

This investigation was supported by U. S. Public Health Service Research Grant HE 10597 from the National Heart Institute.

Materials and Methods

Immunization of Rabbits

Female rabbits of 2 to 3 months of age were used in the present experiments. Their body weight was between 1.0 and 1.5 Kg.

For the active immunization of the animals, the antigens were prepared by the supernatant of the isologous aortic tissue homogenates diluted with saline solution to final concentration of 1 : 20 (w/v) of the original tissue weight (Ao-H). The passive immunization was performed by the injections of the sera obtained from patients with aortitis syndrome (S-Ao-S) with complement fixing anti-aorta antibodies of a high titer.

The animals were divided into 6 groups ; a, b, c, A, B and C (Table I).

Group a : 5 animals receiving 0.2 ml. of S-Ao-S added with an equal volume of Freund's complete adjuvant (F-c-a) into foot pads intracutaneously once weekly for 3 months.

Group b : one animal receiving no immunological procedure for 3 months.

Group c : one animal receiving 0.2 ml. of S-Ao-S intravenously 3 times weekly for 3 months.

Group A : 4 animals receiving the same procedures as those of group a for 12 months.

Group B : 5 animals receiving the same procedures as those of group c for 3 months and receiving 0.2 ml. of the same human serum together with an equal volume of F-c-a once a week into foot pads intracutaneously for the subsequent 9 months.

Group C : 6 animals receiving F-c-a alone into foot pads intracutaneously once a week for 12 months.

Table I. Materials and Methods

Group	No. of Rabbits	Duration (months)	Material			Method	
			Ao-H	S-Ao-S	F-c-a	I/C	I/V
a	5	3	●		●	●	
b	1	3					
c	1	3		●			●
A	4	12	●		●		
B	5	12 (3)		●			●
		12 (9)		●	●	●	
C	6	12			●	●	

Ao-H : Homogenate of rabbit aorta
S-Ao-S : Serum of patient with aortitis syndrome
F-c-a : Freund's complete adjuvant
I/C : Intracutaneous injection
I/V : Intravenous injection

Histological Examination

All animals were sacrificed at the end of experimental period of 3 or 12 months. The aorta, major arteries and several organs (heart, kidney and liver) were fixed in 10% neutral buffered formalin for routine histologic examination, and stained by hematoxylin-eosin, elastica van Gieson and/or Azan stains.

Complement Fixation Test

In groups A, B and C, monthly examination of the sera by complement fixation test was performed for the development of antibody against isologous aortic tissue. The method was based essentially on procedures reported by Ogata.

Results

Histological Findings

In groups a, b and c, histological examination disclosed almost normal findings. In groups A and B, however, there were pathological changes of varying degrees in the aorta and the major arteries. They consisted of fragmentation or distortion of elastic fibers, atrophy or degeneration of muscle fibers, and cellular infiltration in the media. Cellular infiltration or proliferation with or without hemorrhage was found in the adventitia. Distribution of these histological changes is illustrated in Tables II, III and IV. The changes of elastic fibers had tendency to locate in the aortic arch and its

Table II. Change of Elastic Fiber

Location \ Rabbit	A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4	B_5	C_1	C_2	C_3	C_4	C_5	C_6
Aortic arch	++	+++	++	+			+	++			+	+			
Brachiocephalic								+++							
R. common carotid		+		+		++									++
L. common carotid		+	++	+				+++							
R. subclavian	+														
L. subclavian	+			+++											
Pulmonary					+					+					
Descending thoracic aorta							+								
Abdominal aorta						++					+++				
Celiac				+++	++			+	+++						
Superior mesenteric				+++	++			+	+++						
Inferior mesenteric		+													
R. renal															
L. renal									+						
R. iliac									+						
L. iliac							+++								

+ : mild, ++ : moderate, +++ : severe

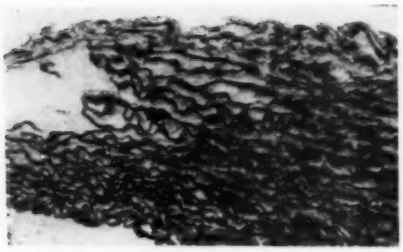


Fig. 1. Fragmentation of elastic fibers and aneurysm of the aortic arch in a case of group A (elastica van Gieson's stain, ×50).

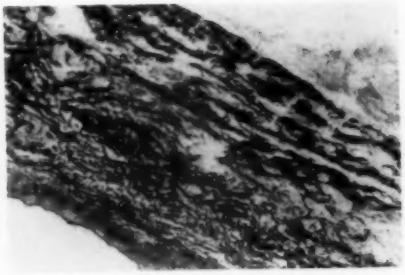


Fig. 2. Fragmentation of elastic fibers of the brachiocephalic artery in a case of group B (elastica van Gieson's stain, ×50).

Table III. Cell Infiltration in the Media and Adventitia

Location \ Rabbit	A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4	B_5	C_1	C_2	C_3	C_4	C_5	C_6
Aortic arch															
Brachiocephalic	+														
R. common carotid															
L. common carotid															
R. subclavian		++ (++)		+					+ (+)						
L. subclavian					+										
Pulmonary								+++							
Descending thoracic aorta															
Abdominal aorta			+												
Celiac				++ (++)				++ (++)							
Superior mesenteric		+	+		++		+	+	++						
Inferior mesenteric															
R. renal								++							
L. renal															
R. iliac															
L. iliac															

+ : mild, ++ : moderate, +++ : severe in the adventitia (and media)

main branches in group A (Table II.) In the aortic arch, these changes were detected in all 4 cases of group A, including 3 cases of moderate or severe changes. In group B, 2 of 5 cases had mild or moderate changes, and in group C, 2 of 6 cases had only mild changes. In both common carotid arteries and both subclavian arteries, these changes had the same tendency. In the main branches of abdominal aorta such as the celiac or superior mesenteric arteries, significant changes were found only in group B. Fig. 1 shows the fragmenta-

tion of elastic fibers and aneurysm of the aortic arch in a case of group A (A_2), and Fig. 2 shows the fragmentation of elastic fibers of the brachiocephalic artery in a case of group B (B_4).

Table III demonstrates cell infiltration in the media and adventitia. It consisted mainly of round cell infiltration. It was not infrequently found in the celiac and superior mesenteric arteries in groups A and B. In group C,

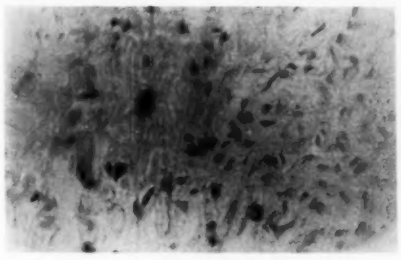


Fig. 3. Cellular infiltration in the media and adventitia of the right subclavian artery in a case of group A (hematoxylin-eosin stain, ×200).

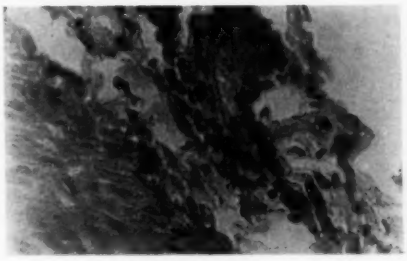


Fig. 4. Cellular infiltration in the adventitia of the pulmonary artery in a case of group B (hematoxylin-eosin stain, ×200).

Table IV. Other Changes in the Arteries

Location \ Changes / Group	Atrophy or degeneration of muscle fiber			Edema in the media			Other changes		
	A	B	C	A	B	C	A	B	C
Aortic arch		1		1	1	1	1*†		
Brachiocephalic									
R. common carotid									
L. common carotid									
R. subclavian	1	1	1				1†		
L. subclavian								1†	
Pulmonary					2				
Descending thoracic aorta									
Abdominal aorta		1						1*†	1†
Celiac	1	2							
Superior mesenteric	1	1							
Inferior mesenteric									
R. renal		1							
L. renal		1							
R. iliac		1							
L. iliac		1							

*: Aneurysm, †: Hemorrhage

however, it was found in none of 6 cases. Fig. 3 shows the cellular infiltration in the media and adventitia of the right subclavian artery in a case of group A (A_2), and Fig. 4 shows the same change in the adventitia of the pulmonary artery in a case of group B (B_4).

Table IV indicates the other changes in the arteries, including atrophy or degeneration of the muscle fiber, edema in the media, aneurysm and hemorrhage. These changes were detected mainly in groups A and B, but were rarely recognized in group C.

Spontaneous aortic lesions such as cartilaginous metaplasia and mesenchymal intimal thickening were detected in some animals.

As shown in Table V, several cases of groups A and B exhibited changes in myocardial tissue such as hyaline-like eosinophilic body, Anitschkow myocyte, and mononuclear cell infiltration. The presence of eosinophils in the left ventricular myocardium was seen in 2 cases of group B. These myocardial changes were absent in group C. Fig. 5 shows eosinophilic body in the left ventricular myocardium in a case of group B (B_1). Fig. 6 demonstrates Anitschkow myocyte in the left ventricular myocardium in a case of group B (B_1).

No significant changes of the liver and kidney were noted in any of these groups.

Changes in Circulating Anti-aorta Antibody Titer during the Experiment (Fig.7 and 8)

The presence of the complement fixing antibodies against the isologous aorta was detected only in group A, and their peak value was observed 2 to 7 months after the beginning of the immunization. For the subsequent months

Table V. Cardiac Changes

Changes \ Location \ Rabbit		A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4	B_5	C_1	C_2	C_3	C_4	C_5	C_6
Eosinophilic body	LA															
	LV		###		+	##	+									
	RV					+										
Anitschkow myocyte	LA															
	LV					##	+									
	RV															
Cellular infiltration	LA			+												
	LV				##			+								
	RV															

+ : mild, ## : moderate, ### : severe
LA : left atrium, LV : left ventricle, RV : right ventricle

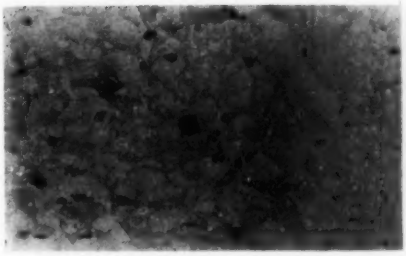


Fig. 5. Eosinophilic body in the left ventricular myocardium in a case of group B (hematoxylin-eosin stain, ×200).

Fig. 6. Anitschkow myocyte in the left ventricular myocardium in a case of group B. Note the caterpillar-like intranuclear structure (hematoxylin-eosin stain, ×200).

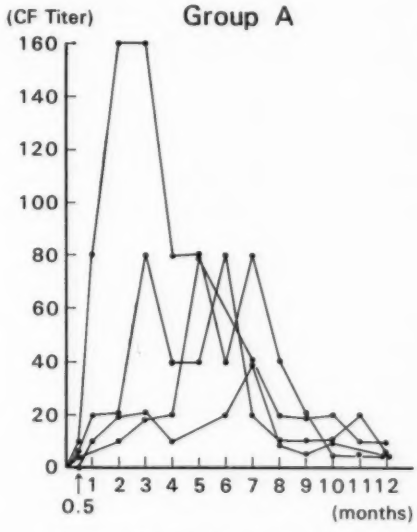


Fig. 7. Changes in the complement fixing antibody titers in group A.

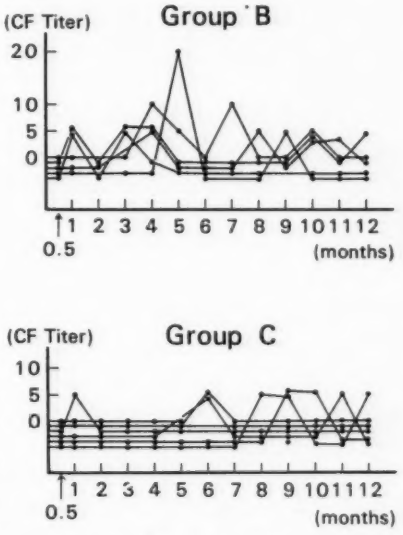


Fig. 8. Changes in the complement fixing antibody titers in groups B and C.

their titers gradually decreased. There was no relationship between the degree of the histological changes and the titer of complement fixing antibodies. No significant rise in the antibody titer was found in groups B and C except for temporary and slight elevation of the titer in a few cases of group B.

Discussion

Many efforts have been made to find methods which might be helpful in the differential diagnosis of vascular diseases. These include clinical, bio-

chemical, histological, immunological and many other methods.

The presence of active antigenic substances in the blood vessels of the rat was shown by Pressman and associates.[2] Piomelli et al.[3] clearly showed the antigenic property of human vessels. More recently, an autoimmune mechanism has been postulated for periarteritis nodosa, anaphylactoid purpura, aortitis syndrome and other forms of vasculitis. Some serological examination such as complement fixation reaction[1),4)] and tanned agglutinin reaction[5)] have been described between the sera of patients with aortitis syndrome or periarteritis nodosa and the extracts of human aorta. A few reports have so far been published, dealing with particular reference to immunofluorescence studies in aortitis syndrome[1),6)] and periarteritis nodosa.[7)] Israel and his associates[8)] injected the serum from patients with vasculitis to guinea pigs and produced the histologic lesions similar to those seen in human vasculitis. They did not, however, deal with the circulating antibody against human vascular constituents.

The present studies showed that isologous extracts of aorta could act as antigens to produce the antibodies and to cause the aortic or arterial lesions, which were similar, at least in part, to those seen in the patients with aortitis syndrome, and that injections of the patients' sera containing anti-aorta antibodies could also produce the similar vascular lesion.

Analysis[13)] of the data of 72 autopsy cases of aortitis syndrome collected from 29 sources throughout Japan showed : 1) edematous fibrosis of the intima, 2) fragmentation of elastic fibers, diffuse fibrosis and chronic proliferative inflammation of the media, and 3) diffuse fibrosis and chronic proliferative inflammation of the adventitia. Distribution of these changes coincided with that of each other.

In Koszewski's case,[9)] acute neutrophilic periarteritis progressed to panarteritis and produced arterial thrombosis. The later stages were characterized by fibroblastic hypertrophy of the adventitia and chronic inflammatory changes of the media and adventitia. In Harbitz's case,[10)] the round cell infiltration in the aortic adventitia was very pronounced. Similar inflammatory changes were present in the carotid and subclavian arteries. Oota[11)] reported a case in which marked fibrosis of the adventitia of the aortic arch and its branches and atrophy of the media were seen. In Frøvig's case[12)] the aorta and its branches revealed massive inflammatory foci in the media and adventitia.

The experimental arterial lesions produced in our present study showed that fragmentation of elastic fiber was marked in the aortic arch and its branches in group A, but that cell infiltration found in groups A and B was of rather mild degree, revealing scattering distribution. The celiac and superior mesenteric arteries were apparently the principal sites affected by cell infilt-

ration in both of these groups. The changes of elastic fiber mentioned above were similar to those seen in human cases of aortitis syndrome. Mild degree of cell infiltration in the same regions might indicate the healed or degenerative stage (inactive stage).

From the facts that the vascular changes found in group A were not seen in group a, which was treated by the same procedures for 3 months, and that the peak value of the complement fixing titier of anti-aorta antibodies in group A was observed 2 to 7 months after the beginning of immunization, it is considered that the rise in the titer of anti-aorta antibodies is not the result but the cause of the vascular changes. In other words, these changes may be attributed to specific antigen-antibody reaction, although no definite relationship was noted between the degree of the vascular lesions and the peak value of the antibody titer. A marked rise in the antibody titer as seen in group A was not recognized in rabbits of group B, in which passive immunization was performed. But, one of them (B_4), in which the changes in elastic fibers and cellular infiltration were most prominent, exhibited a transient rise in the antibody titer, which may be due possibly to an antigenic substance in the patients' sera.

In the present experiments, the rabbits of the control group (group C) received Freund's adjuvant alone. However, more complete control study should include the treatment with the extracts of rabbit tissues other than the aorta as well as the immunization with the normal human serum.

The significance of Anitschkow myocyte and eosinophilic body seen in the myocardial tissues in groups A and B is obscure. Perhaps both are due to reaction against foreign body or to immunological response. Anitschkow myocyte is the characteristic histiocyte of the myocardium and has owl-eyed or caterpillar intranuclear structure. Such an intranuclear structure was found in the myocardial cells of patients who died of active rheumatic heart disease. Hoops and Wissler[14] reported infiltration of large mononuclear cells resembling Anitschkow myocytes in the foci of cystic necrosis in the media of the aorta of a rabbit that was sacrificed a few days after intravenous injections of 2 large doses of horse serum and 2 courses of sulfadiazine treatment by mouth. McKeown[15] sensitized rabbits with intravenous injection of horse serum and found that the commonest change in these rabbits was coronary artery lesions such as inflammatory exudate surrounding and infiltrating the vessels. In addition, small granulomata, very much like Aschoff nodules, were present in the myocardium. These lesions were thought to be identical with those due to rheumatic fever.

Acknowledgement

The authors are indebted to Drs. K. Hirota and K. Iguchi for their valuable advices and to Mr. T. Suzuki for his technical assistance.

References

1. Ueda, H., Saito, Y., Ito, I., Yamaguchi, H., Sugiura, M., and Morooka, S.: Jap. Heart J. **8**: 4, 1967.
2. Pressman, D., Sherman, B., and Korngold, L.: J. Immunol. **67**: 493, 1951.
3. Piomelli, S., Stefanini, M., and Mele, R. H.: J. Lab. Clin. Med. **54**: 241, 1959.
4. Ito, I.: Jap. Circulat. J. **30**: 87, 1966.
5. Ikeda, M.: Jap. Circulat. J. **30**: 75, 1966.
6. Sano, K. and Sito, I.: Neurologia Medico-chirurgica **8**: 28, 1966.
7. White, F. N. and Grollman, A.: Arch. Path. **78**: 31, 1964.
8. Israel, L., Mathe, G., and Bernard, J.: Rev. franç étud. clin. et biol. **1**: 57, 1956.
9. Koszewski, B. J. and Hubbard, T. F.: Circulation **16**: 406, 1957.
10. Harbitz, F.: Arch. Path. **1**: 499, 1926.
11. Oota, K.: Trans. Soc. Path. Japan **30**: 680, 1940.
12. Frǫvig, A. G. and Laken, A. C.: Acta psychiat. et neurol. scandinav., **26**: 313, 1951.
13. Committee Report: Jap. Heart J. **9**: 76, 1968.
14. Hopps, H. C. and Wissler, R. W.: J. Lab. Clin. Med. **31**: 939, 1946.
15. McKeown, E. F.: J. Path. Bact. **59**: 547, 1947.

ABC Electrocardiographic Diagnosis of Ventricular Septal Defect

E. R. Trethewie, M.D.

Summary

ABC-E. C. G.'s in 22 cases of ventricular septal defect (18 pre-operative, 4 post-operative) are analysed.

Right, left and bi-ventricular hypertrophy were correctly assessed electrocardiographically.

Characteristic appearances in Fallot's tetralogy, PS with simple VSD and simple VSD are presented.

The diagnostic value of the ABC tracings is evaluated.

Additional Indexing Words:
Fallot's tetralogy Pulmonary stenosis Patent ductus Coarctation of the aorta Right ventricular hypertrophy Left ventricular hypertrophy Biventricular hypertrophy

IN ventricular septal defect most observers content themselves with assessing some degree of chamber hypertrophy in the E.C.G., either left, right or combined hypertrophy. In many instances the standard 12-lead E.C.G. is normal. RSR[1] forms may be seen in right precordial leads, especially with multiple defects.

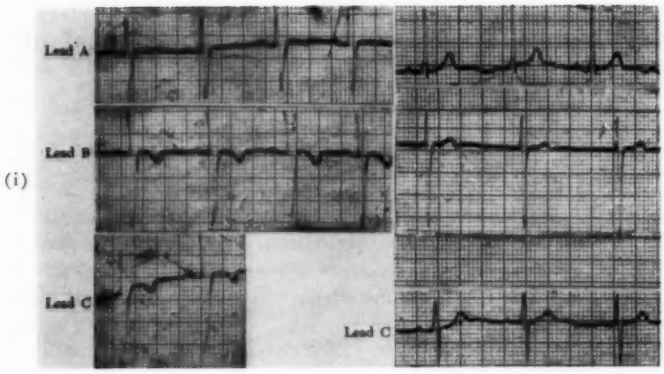
We have observed three types of E.C.G. in the orthogonal ABC leads in ventricular septal defect.

1. Fallot's Tetralogy

Here the right ventricular hypertrophy with pulmonic stenosis is indicated by the very prominent R waves in all leads and virtually absent S waves. In pulmonic stenosis, as an isolated lesion, we have been able to relate the ratio RA/SB (measured in potential) to the actual level of pressure in the right ventricle (Trethewie, 1962) and this also indicates the gradient across the stenosed pulmonary valve or hypertrophied outflow tract in outflow obstruction, since the pulmonary artery pressure in such instances is nearly always in the range 20–28 mm.Hg. In pure pulmonary stenosis, notching of the type now described does not occur.

If one performs a synchronous ABC lead tracing, an upright wave (called upright " Q " wave) is seen in lead B of approximately 0.25 mV. immediately preceding in time the R wave in lead B, which latter corresponds to the R

From the Department of Physiology, University of Melbourne, Parkville 3052, Victoria, Australia.
Received for publication June 5, 1968.



(i) (ii)

Fig. 1. (i) E.C.G. of a normal 7 year old male. Note the potential of S_B namely 1.5 mV. R_A is also of small potential, 0.7 mV. This is normal. $R_A/S_B=0.47$. T_C is of normal shape and inverted. This is not rare in young children. T_B is commonly inverted at any age.

(ii) E.C.G. of a normal male 19 years. Note upright T_A, T_C-normal shape.

waves in leads A and C (Trethewie, 1953). This is a definitive wave and not like the irregular notching seen after cardiac infarction from varying fibrosis. This finding may also occur in lead C. The "Q" wave action current is related to septal contraction and is absent in animals not possessing a septum. In Fallot's tetralogy the membranous septum is almost always involved, though the defect may be of varying size. The aorta over-rides the defect and the septal papillary muscle is involved. Fig. 1 shows ABC tracings of a normal child of 7 years (i) and a youth of 19 years (ii). Fig. 2 a(iv) shows a typical tracing in Fallot's tetralogy.

The thesis is presented that owing to the defect in the ventricular septum, with the close proximity of the bundle tissue, the septal dipoles during contraction are orientated around the deficiency and owing to their displacement the directional vector of the "Q" form of the action current of the septum is abnormal. This yields an upright instead of downward Q wave in lead B. The S wave in left ventricular hypertrophy is a large downgoing wave and in septal activity the Q wave should be downgoing, but owing to the disfiguration the action current at first is reversed directionally. VSD is associated with this change in lead B alone, lead B and C, occasionally in A, B and C, but not in A and B alone. The findings in the 18 pre-operative cases are shown in Table I.

V.S.D. with Pulmonary Stenosis

Ventricular septal defect may be associated with plumonary stenosis where the septal papillary muscle is not involved.

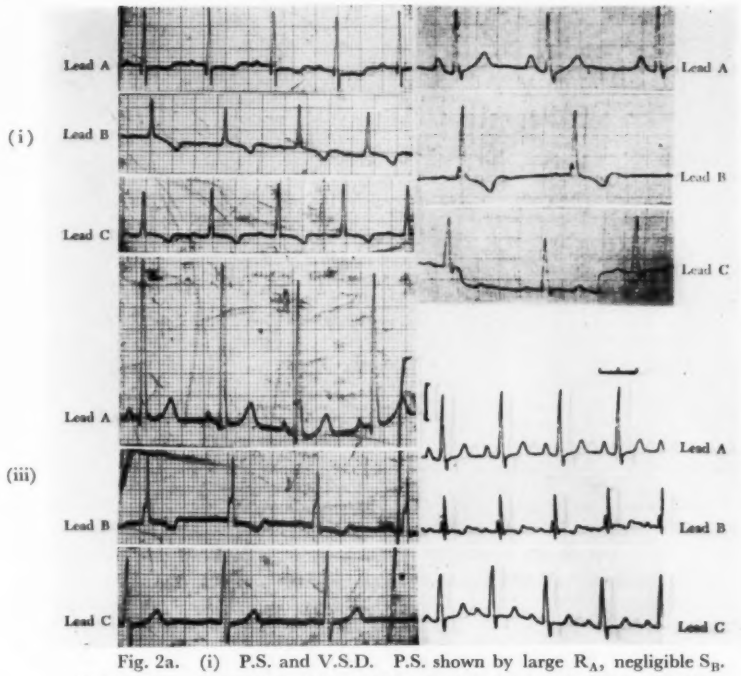


Fig. 2a. (i) P.S. and V.S.D. P.S. shown by large R_A, negligible S_B. V.S.D. shown by small upright "Q" B. R.V.P. 84, L.V.P. 82 mm. Hg. Pre-operative and operative confirmation.

(ii) P.S. and V.S.D. P.S. shown by large R_A, negligible S_B. V.S.D. shown by small upright "Q". Operative confirmation.

(iii) P.S. and V.S.D. P.S. shown by large R_A, negligible S_B. V.S.D. shown by small upright "Q" B. R.V.P. 96 mm. Hg. Operative confirmation.

(iv) Fallot's tetralogy. Female aged 13 years. Details in text.

In these instances the R wave prominence and reduced to negligible S wave of pulmonary stenosis are observed and there is a small-wave notching at the base of the R wave in lead B (Fig. 2a, (i), (ii), (iii)) (Trethewie, 1955). In each of these instances a confident diagnosis of P.S. with V.S.D. may be made. These were all confirmed at operation. The correspondence of upright Q in B (notch at base of the R wave) as a "Q" wave is shown to be aligned (Fig. 3) with the downgoing Q of lead A.

V.S.D. with Patent Ductus

Two cases of V.S.D. occurred in this series associated with patent ductus. While there are no significant changes associated with P.D. other than L. or R.V.H. the V.S.D. appearance is still evident with the notching or step on R_B. This is shown in Fig. 2b, (i) V.S.D. with P. D. and R.V.H. while (ii) shows V.S.D. with P. D. and coarctation of the aorta. Here the S_B

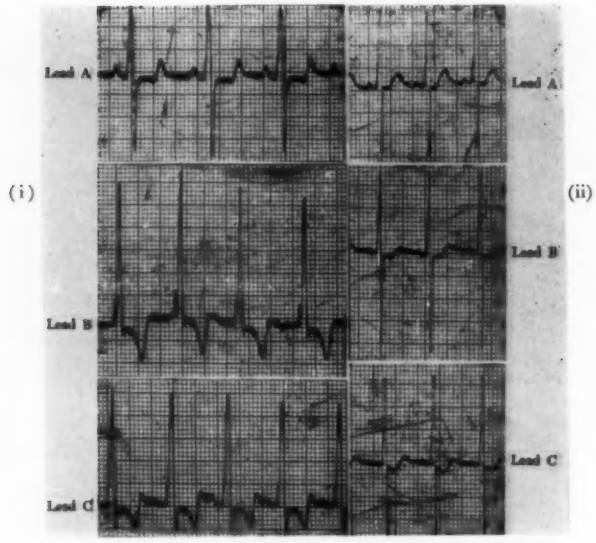


Fig. 2b. (i) P.D. with R.V.H. and V.S.D.
(ii) P.D. with V.S.D. and coarctation of the aorta.

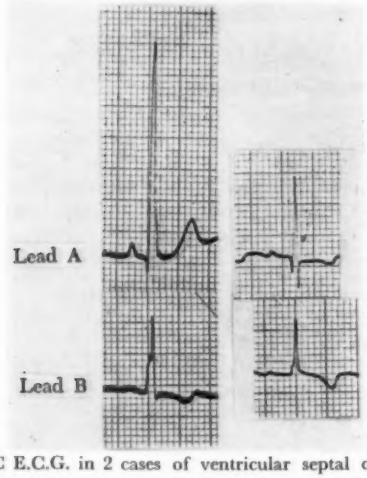


Fig. 3. ABC E.C.G. in 2 cases of ventricular septal defect with pulmonary stenosis. Note large R_A and absent S of severe pulmonary stenosis. Upright "Q" is aligned with "Q" A in timing.

is large 2.2 mV. associated with the L.V.H. of aortic coarctation.

2. *Insignificant V.S.D.*

In a number of instances of small insignificant muscular V.S.D. there is a notched S wave (Fig. 4, (i), (ii), (iii)) in lead B. In this series of 22 con-

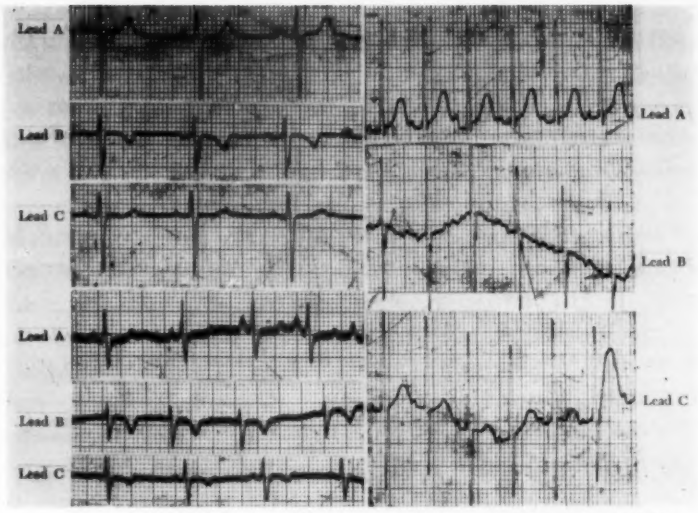


Fig. 4. (i) E.C.G. of child 10 years with small unimportant V.S.D. History, auscultation, X-ray (angiogram) and catheter confirmed.

(ii) E.C.G. of 4 year old male with mild V.S.D. Confirmation by history, auscultation, X-ray.

(iii) Eleven month old baby. Moderate P.S. (large R_A). Probable small V.S.D.—judgment on history, auscultation, X-ray (angiocardiography).

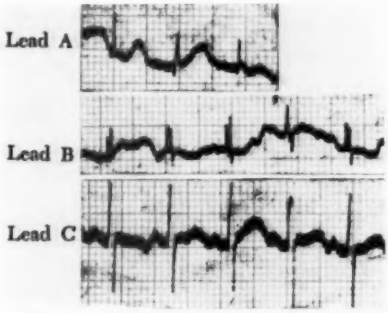


Fig. 5. E.C.G. of child 4 weeks of age—note the prominent upright "Q" wave of V.S.D. Diagnosis confirmed by catheter, angiocardiography.

firmed V.S.D.'s 3 such cases occurred. While this finding is occasionally observed with perfectly normal hearts, when there are auscultatory findings suggestive of V.S.D. it adds to the significance and this association has been described previously (Trethewie, 1968). Further in so-called normals, one cannot be sure a small muscular insignificant V.S.D. is not present since these cases are not fully investigated.

3. In V.S.D. unassociated with pulmonary stenosis an upright Q wave

(R prime), here considered to be an upright Q wave for the reasons elaborated, is observed again in lead B. This occurred in 5 instances in this series. A typical case is shown in Fig. 5, a tracing taken from a child of 4 weeks of age. Catheter and angiocardiography confirmed the diagnosis and operation was deferred because of respiratory illness and age. In some severe instances there is a deep downgoing slurred Q_B wave (ventricular strain) and a slurred R wave.

4. *Absence of notching*

In 4 instances there was no notching at the base of R_B to suggest V.S.D.

Table I. Analysis of 18 Cases of V.S.D. with ABC E.C.G.

Small step on R wave B	Upright R prime $B=Q$	Notched S.B.	Negative
6	5 (one with changes in C also)	3	4 (3 mild, 1 severe)
% approx. 35	30	15	20

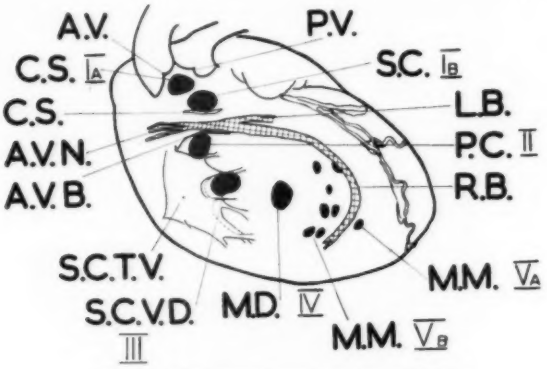


Fig. 6. Diagram of common sites of V.S.D.

A.V.	Aortic valve
C.S. IA.	Conus septal defect
C.S.	Crista supraventricularis
AVN	Atrio ventricular node
AVB	Atrio ventricular bundle
SCTV	Septal cusp tricuspid valve
SCVD 111	Septal cusp ventricular defect
MD IV	Muscular defect
M.M. Va	Muscular defect
M.M. Vb	Multiple muscular defect
R.B.	Right bundle
L.B.	Left bundle
P.C. II	High posterior defect
L.B.	Left bundle
S.C. IB	Conus defect
P.V.	Pulmonary valve

Two of these were minor negligible V.S.Ds. not requiring treatment, one was a high V.S.D. and one was an apical muscular V.S.D. (see Table I). In the conus (high) septal-defect the bundle tissue and action current in the septum cannot be expected to be affected because the bundle tissue and action current associated with the septal event are clear of the lesion (Fig. 6). In the apical V.S.D. this part of the septum contracts almost simultaneously with the ventricular apex and in this case there can only be negligible slurring.

When notching occurs only in leads A and B the above conclusions do not apply, because leads B and C are more definitive of septal events than lead A. The case is then to be regarded as one of partial block and possibly associated with a strain pattern but it is not of diagnostic significance in V.S.D.

Notching may not be apparent with a heat writer when it is readily apparent with a cathode ray oscilloscope. Such a case regarded as negative notching may on heat writer amplification (Fig. 7) show the second wave to be evident by the broad base of the R in B and the fusion of the wave at the summit with the rise of the R wave. This appearance has been shown in the special configuration of atrial septal defect to form a classical step-wave on the oscilloscope (Lewis and Trethewie, 1954).

Chamber hypertrophy:

In 6 instances the E.C.G. indicated there was normal R and L ventricu-

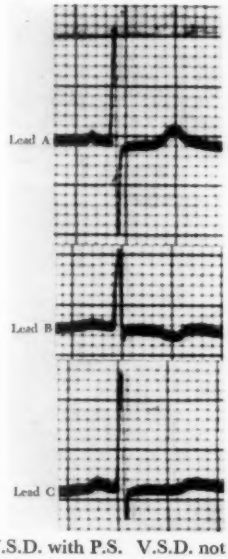


Fig. 7. E.C.G. of V.S.D. with P.S. V.S.D. not indicated in normal heart tracing—amplification (2×) shows broad base of R_B with apex of " upright " Q fused with ascending limb of R_B.

Table II. Chamber Hypertrophy in ABC Leads in 18 V.S.D. 's (pre-operative)

Normal R and L Pressures	RVH (Right Ventricular Hypertrophy)	LVH (Left Ventricular Hypertrophy)	R and LVH (Bi-Ventricular Hypertrophy)
E.C.G. 6	6	4	2
Catheter: 4 confirmed 2 not measured	5 confirmed 84, 96, 106, 131, 140 mm.Hg one not measured.	2 confirmed 131, 119 mm.Hg 2 not measured	Both confirmed R/L * 68/85, 108/124 mm.Hg
35%	35%	20%	10%

* Coronary cusp aorta, conus S.D. Blood pressure (brachial) in ward elevated (124 mm.Hg) A.I.

lar pressure. In 4 instances this was confirmed by cardiac catheter. In 2 it was not measured.

Right ventricular hypertrophy was observed in 6 instances (Table II) by electrocardiography $\left(\frac{1}{R_A/S_A+R_A/S_B}=0.0-0.08 \text{ in this series}\right)$ (normal 0.4–0.9 in this series. In one instance, a baby 4 weeks old, this ratio was 0.1, but R_A was quite small and within normal limits, namely 0.35 mV.). In 5 of these the pressure was measured and found to be 84, 96, 106, 131 and 140 mm. Hg. In the 6th instance it was not measured.

In 4 instances, the E.C.G. indicated left ventricular hypertrophy (S_B 4 mV., 5 mV., 3 mV., 4 mV.), (normal 1–1.5 mV.) (Trethewie, 1968). In 2 of these instances this was confirmed by catheter (131, 119 mm.Hg) and in the remaining 2 it was not measured. In L.V.H. the above ratio was 0.89–2.5.

In 2 instances there was biventricular hypertrophy by ABC analysis (R_A 3 mV., 3.5 mV., S_B 7.6 mV., 4.5 mV. respectively) and both were confirmed by catheter sutdy (68, 124 mm.Hg, 108, 124 mm.Hg respectively). With B.V.H., the above ratio was 0.44 and 0.49.

Upright " Q " wave

That the R wave forms appearing like RSR^1 is actually an upright " Q "

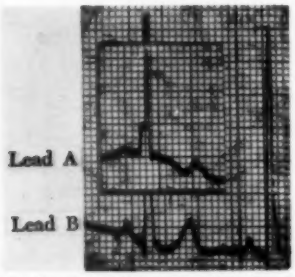


Fig. 8. E.C.G. of P.S. with V.S.D. Lead B placed over lead A—upright " Q " B aligns with " Q " A.

is shown by the tracing of Fig. 8. This shows lead B overlaid on lead A (pulmonary stenosis, muscular V.S.D.) and the notch at the base of R_B lines up with Q_A. This timing indicates " R " is a septal event and is in fact due to a V.S.D. altering the orientation of the muscular excitation wave. The comparison of P- upright " Q " and PR interval is shown in Table III.

In one instance the E.C.G. diagnosis was incorrect. The report was " I have not seen this constellation before (notching includes R_A as well without R_C) but I would consider the child has pulmonary stenosis, which is definite

Table III. P– " Upright " Q Interval B, Related to P–R Interval A

Subject No.	P–"Q"$_B$	P–R_A	P–"Q"$_A$
13	0.16″	0.20″	0.16″
14	0.10	0.12	0.10
15	0.10	0.14	0.10
16	0.13	0.16	0.13

That this upright wave in B is a "Q" is indicated by the timing. It occurs at the time of the "Q" wave in lead A.

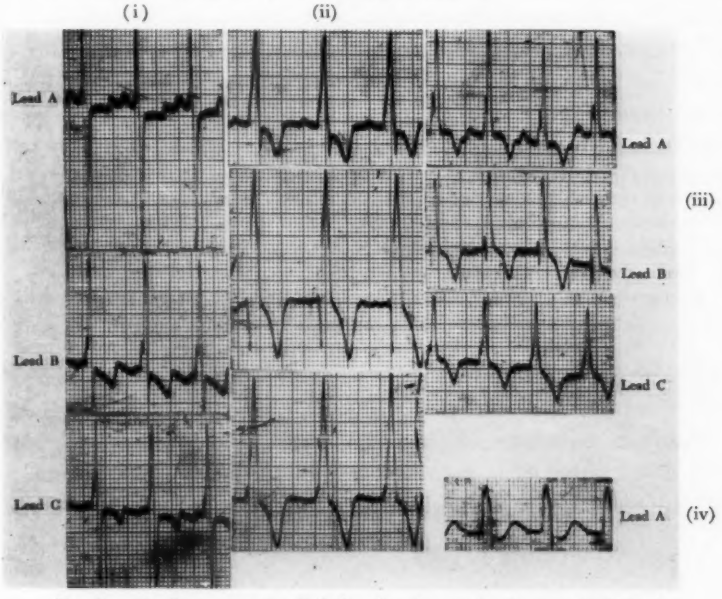


Fig. 9. (i) Post-operative E.C.G. Simple repair of muscular V.S.D. Note the upright " Q " B.

(ii), (iii) and (iv): Block pattern following operation—patch repair, (ii), transatrial closure (iii), patch V.S.D. (iv). Typical R.B.B. patterns following extensive operative septal suture.

(R.V.P. about 140 mm.Hg) and probably also a V.S.D. which is high up near the atrium." At operation pulmonary stenosis (RVP 131 mm.Hg) was found but no V.S.D. Since I have never seen a preoperative V.S.D. with notching in RA and RB and not in RC, this was an incorrect assumption.

Post-operative appearance of ABC E.C.G.:

Postoperatively in 1 of 4 instances the E.C.G. was typical of V.S.D. preoperatively. There was an upright Q wave, 0.5 mV. against R_B and an upright "Q" wave 0.4 mV. against R_C (Fig. 9 (i)). This patient, operated on 6 months previously, had a simple repair of a simple muscular V.S.D. In the other 3 instances a gross right bundle block obscured any diagnosis (Fig. 9 (ii), (iii), (iv)). Two were Fallot's tetralogy with a patch repair and a transatrial closure of the V.S.D. and the other was a patch repair of a severe V.S.D. The suture must, in these instances, affect bundle distribution in the septum and account for the block pattern.

Acknowledgment

Thanks are due to Dr. Sloman of the Royal Melbourne Hospital and to Dr. Gadboys, Dr. Grishaman, Dr. Litwak, and Dr. Steinfield of the Mt. Sinai Hospital, New York for much assistance.

References

1. Lewis, J. and Trethewie, E. R.: Unpublished experiment. 1954.
2. Trethewie, E. R.: Simplified Electrocardiography. Melbourne University Press. 1953.
3. Trethewie, E. R.: Med. J. Aust. **1**: 789, 1955.
4. Trethewie, E. R.: Cardiologia **40**: 316, 1962.
5. Trethewie, E. R.: Cardiologia **43**: 170, 1963.
6. Trethewie, E. R.: Atlas of ABC Electrocardiography. S. Karger, Basle, Switzerland, 1968.

Special Article

A Reappraisal of Atrioventricular Dissociation*

Edward K. Chung, M.D., F.A.C.C.**

FOR many years confusion has existed regarding the precise definition and terminology of atrioventricular (A-V) dissociation. There are many publications[1)–7)] relating to the subject. Cushny,[1)] in 1897, first demonstrated digitalis-induced A-V dissociation experimentally in the dog. A similar experiment was performed in 1906 by Von Tabora.[2)] Characteristic of the confusion, is whether or not complete A-V block should be included in complete A-V dissociation. However, the term "complete A-V dissociation" has more clarify than that of "incomplete A-V dissociation", which has been alluded to as "interference-dissociation", "dissociation with interference", "A-V dissociation with captured beats" and "incomplete A-V dissociation".[1)–7)] Some investigator differentiated complete A-V block from complete A-V dissociation by simply stating that the atria beat faster than the ventricles in the former and vice versa in the latter. Such a definition is erroneous because complete A-V block is one of the important causes of complete A-V dissociation and the above mentioned relationship is not always true.

Definition

By definition, A-V dissociation indicates that the atria and ventricles beat independently, so that P-waves and QRS complexes do not have constant relationship on the electrocardiogram. The various etiologies responsible for the development of A-V dissociation are illustrated in Diagram 1. It should be emphasized that A-V dissociation is by no means a simple arrhythmia and it is always a consequence of some other cardiac mechanism.

* From the Heart Station and the Department of Medicine, West Virginia University School of Medicine, Morgantown, West Virginia.

** Associate Professor of Medicine, Physician-in-charge, Electrocardiographic Laboratory.

Received for publication August 24, 1968.

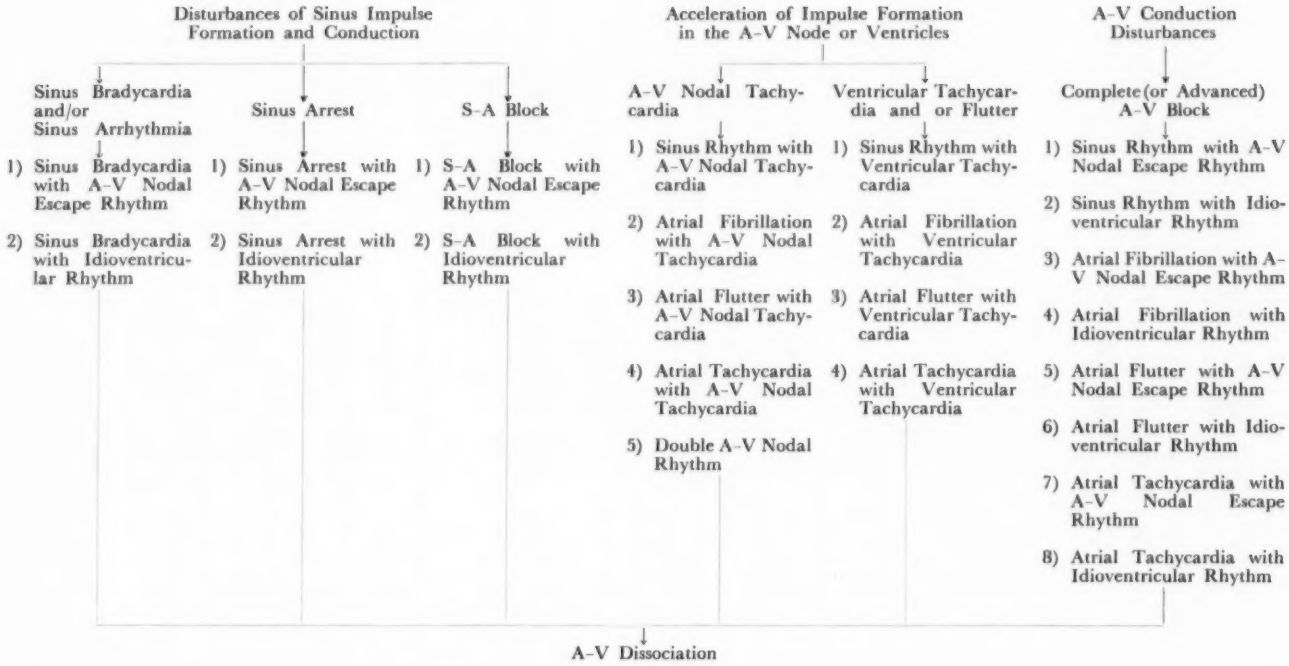

Disturbances of Sinus Impulse Formation and Conduction
Sinus Bradycardia and/or Sinus Arrhythmia
1) Sinus Bradycardia with A-V Nodal Escape Rhythm
2) Sinus Bradycardia with Idioventricular Rhythm
Sinus Arrest
1) Sinus Arrest with A-V Nodal Escape Rhythm
2) Sinus Arrest with Idioventricular Rhythm
S-A Block
1) S-A Block with A-V Nodal Escape Rhythm
2) S-A Block with Idioventricular Rhythm
Acceleration of Impulse Formation in the A-V Node or Ventricles
A-V Nodal Tachycardia
1) Sinus Rhythm with A-V Nodal Tachycardia
2) Atrial Fibrillation with A-V Nodal Tachycardia
3) Atrial Flutter with A-V Nodal Tachycardia
4) Atrial Tachycardia with A-V Nodal Tachycardia
5) Double A-V Nodal Rhythm
Ventricular Tachycardia and or Flutter
1) Sinus Rhythm with Ventricular Tachycardia
2) Atrial Fibrillation with Ventricular Tachycardia
3) Atrial Flutter with Ventricular Tachycardia
4) Atrial Tachycardia with Ventricular Tachycardia
A-V Conduction Disturbances
Complete (or Advanced) A-V Block
1) Sinus Rhythm with A-V Nodal Escape Rhythm
2) Sinus Rhythm with Idioventricular Rhythm
3) Atrial Fibrillation with A-V Nodal Escape Rhythm
4) Atrial Fibrillation with Idioventricular Rhythm
5) Atrial Flutter with A-V Nodal Escape Rhythm
6) Atrial Flutter with Idioventricular Rhythm
7) Atrial Tachycardia with A-V Nodal Escape Rhythm
8) Atrial Tachycardia with Idioventricular Rhythm
A-V Dissociation

Diagram 1. Causes of A-V Dissociation.

Classification and Clinical Significance

The following basic disorders produce A-V dissociation:

1) Disturbances of sinus impulse formation and conduction:

The inherent rate of the primary pace maker (sinoatrial node) in normal adults is 60 to 100 per min., that of the A-V node 45 to 55 and the ventricles 30 to 40.[7),8)] Whenever the primary pacemaker produces an impulse slower than usual (sinus bradycardia and sinus arrhythmia) or fails to conduct impulses to the A-V node due to block at the sinoatrial junctional tissue (sino-atrial block) or fails to produce an impulse (sinus arrest or pause), the A-V node or ventricles may "take over", producing A-V nodal escape or idioventricular rhythm respectively. Almost always, in this situation, A-V nodal escape rhythm appears because of a faster inherent rate in the A-V node as compared with the ventricles.

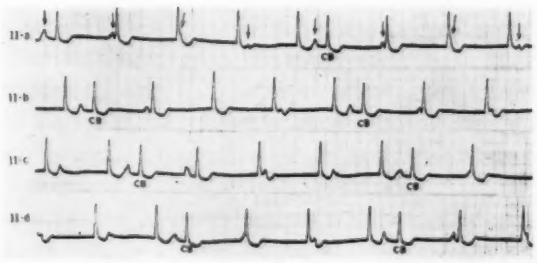


Fig. 1. Lead II-a, b, c, and d are continuous. Arrows indicate P-waves and CB indicates ventricular captured beat. The rhythm is incomplete A-V dissociation characterized by sinus bradycardia (47 per min.) and A-V nodal escape rhythm (53 per min.).

The atria and ventricles would beat independently but at a similar rate, if the rate of the primary pacemaker slowed to the level of A-V nodal escape rhythm (Fig. 1). This type of A-V dissociation may be observed in healthy young adults without any evidence of heart disease. On the other hand, it may be observed during the administration of various drugs including digitalis, reserpine and guanethidine. It has little clinical significance. However, if the mechanism is sinus arrest or sinoatrial (S-A) block, it is always due to serious cardiac disease, such as acute diaphragmatic myocardial infarction, acute myocarditis etc. or intoxication due to various drugs, particularly digitalis.[9)] A-V dissociation almost always appears but as a temporary phenomenon when intermittent and brief sinus arrest or S-A block occurs. For a similar reason, A-V dissociation may temporarily develop following the pause after any premature ectopic impulse, when A-V nodal escape beats appear to control the ventricles. However, one of the lower pacemakers (A-V node or ventricles)

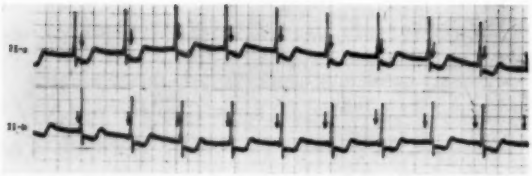


Fig. 2. Lead II-a and b are continuous. Arrows indicate P-waves having no consistent relationship to the QRS complexes. The rhythm is complete A-V dissociation due to A-V nodal tachycardia with a ventricular rate of 72 per min.

may take over the entire cardiac activity, if S-A block or sinus arrest persists for a long period of time.

2) Acceleration of impulse formation in the A-V node or ventricles:

In this instance, the sinus node produces cardiac impulses as usual but the A-V node or ventricles initiate impulses at a faster rate, thus resulting in A-V dissociation (Fig. 2). Rapid ectopic pacemaker action may appear on the electrocardiogram as a paroxysmal or non-paroxysmal tachycardia. Paroxysmal A-V nodal tachycardia may occur in healthy individuals and have almost the same clinical significance as sinus tachycardia. Non-paroxysmal A-V nodal tachycardia is almost always found in heart disease such as rheumatic carditis, acute diaphragmatic myocardial infarction or digitalis intoxication.[8),9)] The heart rate in this arrhythmia ranges between 70 and 130 per min.[8)–19)]

Ventricular tachycardia and rarely flutter may be associated with A-V dissociation but it is quite difficult and often impossible to detect atrial activity (either sinus or ectopic) because during paroxysms, the atrial waves are usually superimposed on bizzare and wide QRS complexes. Ventricular tachycardia associated with A-V dissociation, needless to say, is almost always indicative of serious heart disease and/or drug intoxication particularly the cardiac glycosides.[9)]

3) Atrioventricular (A-V) conduction disturbances:

Whenever the sinus impulse is not conducted to the A-V node and ventricles due to a block in the A-V junctional tissue, the common bundle or bilateral bundles, A-V nodal escape rhythm or idioventricular rhythm develops to control the ventricles as a physiologic mechanism. In this instance, the atrial rate is faster than and also independent of the ventricular rate (Fig. 3). Often, A-V block and S-A block develop in the same patient. This is particularly common in acute diaphragmatic myocardial infarction and digitalis intoxication.[8)–10)] In addition, complete A-V block may develop during acute rheumatic fever, subacute bacterial endocarditis, measles, mumps, various other viral infections, typhus, coronary artery disease without infarction, anoxia

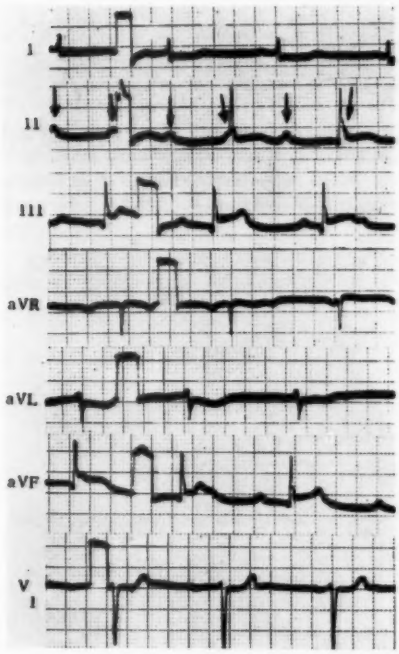


Fig. 3. Arrows indicate P-waves in lead II. This tracing exhibits sinus rhythm (rate : 98 per min.) with A-V nodal escape rhythm (rate : 55 per min.) due to complete A-V block producing complete A-V dissociation. In addition, there is slight S-T segment elevation in leads III and aV_F due to diaphragmatic subepicardial injury.

from anesthesia, pulmonary embolism, shock, various primary myocardial diseases, such as amyloidosis and idiopathic cardiomyopathy and various congential heart disease.[11] Congenital complete A-V block has also been reported.[12]

Captured Bearts: If the mechanism of A-V dissociation is not complete A-V block, whenever any chamber is in the non-refractory state, one of the two pacemakers may activate the entire heart. In other words, the sinus pacemaker may control the ventricles when the latter are not in a refractory phase. This is termed ventricular captured beats[7] (Fig. 1). Likewise, an ectopic pacemaker in the A-V node or ventricles which controls the ventricles may activate the atria in a retrograde fashion when the latter are not in a refractory phase. This phenomenon is termed atrial captured beats[4] (Fig. 4). Ventricular captured beats occur more frequently than atrial because retrograde activation is more difficult physiologically than forward conduction.[7] If the captured impulse in the atria or ventricles simultaneously meets with an impulse

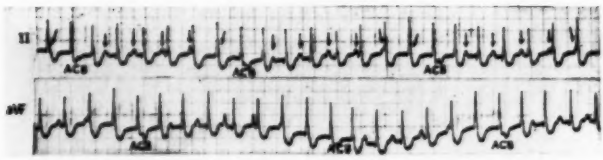


Fig. 4. The tracing shows sinus tachycardia and A-V nodal tachycardia, producing incomplete A-V dissociation. ACB indicates atrial captured beat.

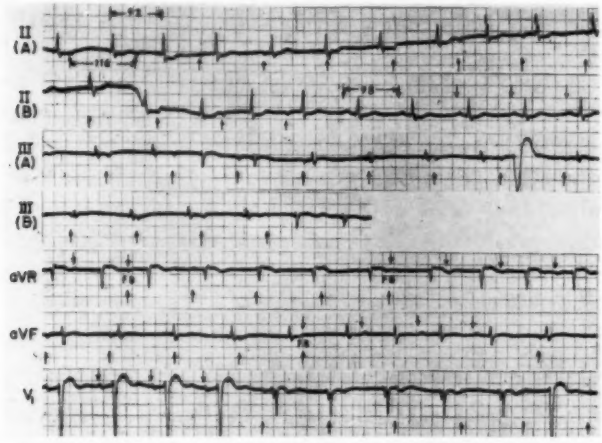


Fig. 5. The tracing shows predominantly double A-V nodal rhythm and an area of sinus rhythm with intermittent A-V dissociation. Downwardly directed arrows indicate sinus P-waves, while upwardly directed arrows (group A) indicate retrograde P-waves. The sinus P-P interval is 0.98 sec.: the retrograde P-P interval, 1.16 sec.; and the R-R interval of the group B nodal rhythm is 0.92 sec. Note the occasional atrial fusion beats in leads aV_R and aV_F (marked FB). The QRS complex of the tenth beat in lead V_1 is most likely a conducted beat originating from the group A nodal pacemaker.

from another pacemaker, partial captured beats develop and this phenomena may be referred to as ventricular or atrial fusion beats (Fig. 5). Recognition of captured beats is not difficult because they occur prematurely with a constant P-R or R-P relationship (Fig. 1). Often, captured beats exhibit aberrant ventricular conduction because of a short coupling interval. Once a captured beat occurs one pacemaker may control the entire heart either temporarily or continuously (Fig. 5). In any event, whenever a captured beat (either complete or partial) is present, this should be termed as " incomplete A-V dissociation " because the atria and ventricles have some relationship to each other even though only momentarily. This has also been called " interference dissociation ", " dissociation with interference " and "A-V dissociation with captured beats ".[1)–7)] In the presence of intermittent complete A-V block,

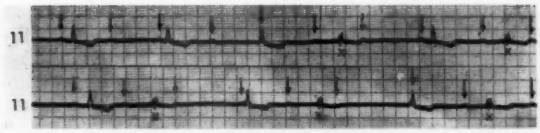


Fig. 6. Arrows indicate P-waves. This tracing shows sinus arrhythmia (rate: 73 per min.) with intermittent A-V nodal escape beats (rate: 40 per min.) due to high degree A-V block producing incomplete A-V dissociation. There are occasional ventricular captured beats with long P-R intervals (indicated x).

captured beats may intermittently occur and this situation has been called " high degree or advanced A-V block " or " almost complete A-V block " (Fig. 6). This is also a form of incomplete A-V dissociation.

If there are no captured beats, and the atria and ventricles beat independently throughout, this should be called " complete A-V dissociation ".[3),4),7)] It should be noted that complete A-V dissociation may be shown to be incomplete if a longer strip is available and the mechanism is not complete A-V block.

Ectopic Atrial Mechanism in A-V Dissociation

In A-V dissociation the atria are not necessarily controlled by the sinus mechanism and likewise the ventricles may be controlled by either the A-V node or the ventricles themselves. Therefore, the atrial mechanism may be either atrial fibrillation, atrial flutter or atrial tachycardia. Under these circumstances, either complete or incomplete A-V dissociation may develop. For example, there may be present atrial fibrillation with A-V nodal escape rhythm or idioventricular rhythm due to complete A-V block (Fig. 7). Atrial

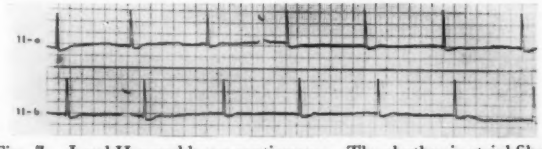


Fig. 7. Lead II-a and b are continuous. The rhythm is atrial fibrillation with A-V nodal escape rhythm due to complete A-V block resulting in complete A-V dissociation.

fibrillation with A-V nodal tachycardia or ventricular tachycardia without A-V block (Fig. 8) may also be present.

If an exit block in varying degree is present below the ectopic pacemaker in the A-V node, the ventricular action may show or become irregular (Fig. 9). When the exit block is of the Wenckebach type, the cardiac rhythm will show

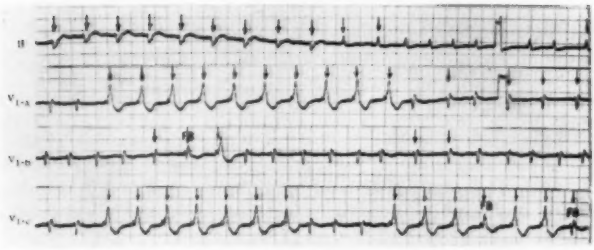


Fig. 8. Lead V_1-a, b and c are continuous. FB indicates ventricular fusion beat. The rhythm is atrial fibrillation with A-V nodal tachycardia (indicated arrows) with aberrant conduction (rate: 123 per min.) resulting in incomplete A-V dissociation.

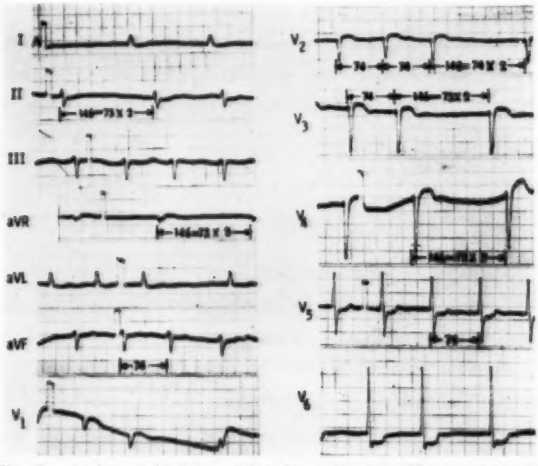


Fig. 9. Atrioventricular nodal tachycardia (rate 83 per min.) with intermittent 2 : 1 exit block and atrial fibrillation producing incomplete A-V dissociation. Numbers represent hundredths of a second.

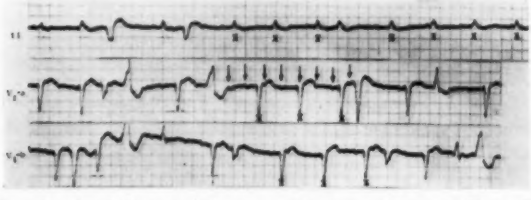


Fig. 10. Lead V_1-a and b are continuous. Arrows indicate P-waves. Tracing shows atrial tachycardia (rate: 180 per min.) and atrioventricular nodal tachycardia (rate: 74 per min.) producing complete atrioventricular dissociation and frequent multifocal ventricular premature beats. (In lead II: third, fifth and ninth beat, V_1-a: third, fourth, sixth, tenth, and twelfth, V_1-b: second, fourth, fifth, seventh, eleventh, thirteenth, and fourteenth).

regular irregularity. Occasionally, further acceleration of A-V nodal impulse formation will occur particularly in the presence of atrial fibrillation. This results in bidirectional A-V nodal tachycardia. This arrhythmia is almost pathognomonic of digitalis intoxication during digitalis therapy.

Atrial tachycardia and A-V nodal tachycardia may co-exist producing so called "double supraventricular tachycardia"[9),13)] (Fig. 10). The above mentioned types of A-V dissociation have been frequently found in patients with digitalis intoxication.[9)]

Double A-V Nodal Rhythm or Tachycardia

In a rare form of A-V dissociation, the atria and ventricles are controlled by two different pacemakers located at the A-V junctional tissue (Fig. 11). In this instance the atria are activated in retrograde fashion. Occasionally,

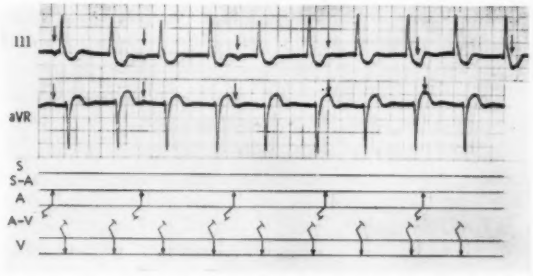


Fig. 11. Complete A-V dissociation due to double A-V nodal rhythm without sinus activity. Arrows indicate retrograde P-waves. The atrial rate is 40 per min. (A-V nodal escape rhythm), and the ventricular rate is 78 per min. (nonparoxysmal A-V nodal tachycardia).

the atria may be intermittently activated by the sinus node in the presence of double A-V nodal rhythm or tachycardia resulting in triple rhythm (Fig. 5). In this case, atrial fusion beats may be observed, placed between antegrade sinus and retrograde A-V nodal impulses (Fig. 5). Each pacemaker at the A-V junction may produce an A-V nodal escape rhythm or A-V nodal tachycardia but in the majority of the reported cases in the literature, the lower A-V nodal pacemaker induced a more rapid rate than the upper pacemaker.[8)] In double A-V nodal rhythm or tachycardia, the pacemaker activating the atria is probably located in the upper portion of the A-V node whereas the pacemaker activating the ventricles is most likely located in the lower portion of the A-V node. Digitalis intoxication is the most common cause of double A-V nodal rhythm or tachycardia.[9)]

References

1. Cushny, A. R.: J. Exp. Med. **2**: 233, 1897.
2. Von Tabora, D.: Ztschr. exper. path. Therap. **3**: 499, 1906.
3. Pick, A.: Am. Heart J. **66**: 147, 1963.
4. Marriott, H. J. L., Schubart, A. F., and Bradley, S. M.: Am. J. Cardiol. **2**: 586, 1958.
5. Scherf, D. and Cohen, J.: The Atrioventricular Node and Selected Cardiac Arrhythmias. Grune and Stratton, New York, 1964.
6. Katz, L. N. and Pick, A.: Clinical Electrocardiography. Part 1. The Arrhythmias. Lea and Febiger, Philadelphia, 1958.
7. Massie, E. and Walsh, T. J.: Clinical Vectorcardiography and Electrocardiography. The Year Book Publishers, Inc., Chicago, 1960.
8. Chung, K. Y., Walsh, T. J., and Massie, E.: Jap. Heart J. **5**: 171, 1964.
9. Chung, E. K.: Digitalis Intoxication (Monograph), Excerpta Medica Foundation, The Netherlands, 1968 (in press).
10. Pick A., Langendorf, R., and Katz, L. N.: Circulation **24**: 12, 1961.
11. Bellet, S.: Prog. Cardiovas. Dis. **2**: 691, 1960.
12. Lev, M.: Prog. Cardiovas. Dis. **6**: 317, 1964.
13. Chung, K. Y. and Thomas, J.: Geriatrics **20**: 1006, 1965.

Case Report

Isolated Levocardia with Polysplenia in an Aged with Special Reference to Minor Cardiac Abnormalities

Masaya SUGIURA, M.D., Ryozo OKADA, M.D.,
and Keisuke HIRAOKA, M.D.

SUMMARY

A world-oldest necropsy case of the isolated levocardia with situs inversus abdominalis and polysplenia was presented. The case was 75-year-old female, who died of bronchopneumonia and cerebral thrombosis. The heart showed rather symmetrical architecture, that is, (1) almost same level of mitral and tricuspid ring and therefore absence of atrial part of the pars membranacea, (2) an anomalous muscle bundle in the left ventricle simulating the crista supraventricularis and (3) symmetrical course of the conduction system in the central fibrous body.

Thirty-one cases with combination of levocardia and situs inversus abdominalis in Japanese literatures were reviewed. Only 2 of them had grossly normal hearts and the others had major anomalies incompatible to long survival.

Additional Indexing Words :

Levocardia Situs inversus Polysplenia Gerontology Congenital heart disease Abnormal muscle bundle in the left ventricle Symmetrical heart Conduction system

LEVOCARDIA with total or partial inversion of abdominal viscera is a relatively rare anomaly and commonly complicated with major congenital heart disease such as truncus arteriosus, transposition of the great vessels, pulmonary stenosis, common atrioventricular orifice, atrial septal defect, ventricular septal defect and so on.[1),2)] Asplenia[3),4)] and polysplenia[5)] are also frequently associated with major cardiac malformations. Such a case hardly survives beyond childhood due to hemodynamic disturbances.

This is a report of a case of isolated levocardia with situs inversus and polysplenia found in an aged woman. In spite of coexistence of situs inversus abdominalis and polysplenia, it was noteworthy that no major anomaly of the heart was found in our case. Instead, minor anomalies in the heart suggesting

From the Department of Internal Medicine, Yoiku-in Hospital, Tokyo Municipal Home for the Aged, Itabashi, Tokyo.

Received for publication June 1, 1968.

more symmetrical architecture than usual were recognized. The symmetrical architecture seen in the ventricles and the conduction system would be valuable to clarify pathogenesis of this kind of anomalies and should be emphasized as their "forme fruste." A total of 31 reported cases in Japan were also reviewed and discussed.

Case Report

A 75-year-old woman (T.I.) entered the Yoiku-in Hospital in March, 1967, because of gait disturbance and speech disturbance of recent development. She had developed normally from her childhood and experienced no particular diseases until June, 1963, when she suffered from the first attack of cerebral vascular disease, followed by an uneventful recovery. In December 1963, X-ray films of the chest and the upper gastrointestinal series revealed that her stomach was on the right side, despite the usual cardiac position. On her admission, her general status was poor with right hemiparesis, incontinentia urinae, and gait and speech disturbances. Percussion of the chest revealed a slightly enlarged heart by one finger breadth to the left and there was a 1/6 systolic murmur of ejection type at the apex. Liver, spleen and kidneys were not palpable. The chest X-ray film (Fig. 1) showed a slightly enlarged heart, stomach fornix below the right diaphragm, and no abnormalities in the lung fields. Electrocardiogram (Fig. 2) showed a development of rsr′ pattern in leads V_1 to V_3 in March, 1967. There were depression of ST segment in leads V_4 and V_5, and marked inversion of the T waves in leads II, III, aV_F and V_1 to V_4. Her

Fig. 1. Chest X-ray film. Note normal position of the heart and inverted position of the stomach fornix (arrow).

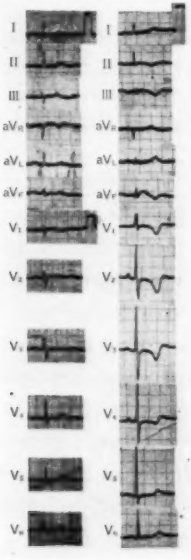


Fig. 2. Electrocardiogram.

clinical course was complicated by fever, cough and sputa with increasing dry and moist rales in the bilateral lung fields, and died on April 6, 1967, despite an intensive treatment with various antibiotics. Clinical diagnoses were (1) situs inversus with levocardia, (2) right hemiparesis due to cerebral thrombosis and (3) bronchopneumonia.

Autopsy findings: Both lungs had 3 lobes. The liver was symmetrical in shape and situated in the middle of upper abdomen, and the gallbladder was also on the center line. Three spleens (25 Gm., 10 Gm. and 5 Gm. each) were present in the right side. The stomach, duodenum and pancreas were inverted completely to the right side with mesenterium commune. Pyloric ring of the stomach was absent.

Heart weighed 340 Gm. and the anterior descending branch of the coronary artery had a marked stenosis up to 75% at the stem and some scattered myocardial fibrosis at the anterior wall. Gross findings of the heart showed no abnormalities in its location and in the relative position of 4 chambers and the great vessels. Cardiac shape was peculiar with a protruded shoulder of the right ventricle, which seemed to be situated relatively high as compared to the left ventricle (Fig. 3a). Right atrium and ventricle showed a slight dilatation and hypertrophy, and the pars membranacea of the interventricular septum was normal in size but located completely below the tricuspid ring (Fig. 3b). When viewed from the left ventricle, the pars membranacea was in normal position. There was an anomalous muscle bundle situated between conus and sinus portions of the left ventricle and projected to the anterior wall from the ventricular septum (Fig. 3c).

Fig. 3. Gross view of the heart.
a. Frontal view. Protruded shoulder of the right ventricle is noted.
b. Rgith side of the heart. Arrow indicates abnormal position of the pars membranacea.
c. Left side of the heart. Arrow indicates the anomalous muscle bundle in the left ventricle.

The conduction system was studied histologically by serial sectioning. Muscle cells in the A-V node were scattered widely to the left beyond the center line with abundant adipose tissue therearound, which should be normally located at the right side (Fig. 4a, b). The bundle of His of normal size penetrated through the central fibrous body nearly on the center line (Fig. 4a, c). Distal to the bifurcation the right bundle branch narrowed itself extremely for length of 5 mm. and went around the lower margin of the pars membranacea of the interventricular septum (Fig. 4a, d), then descended down forming a loop at a sharp angle. The left bundle branch ran almost in normal manner but some of its fibers entered into the anomalous muscle bundle.

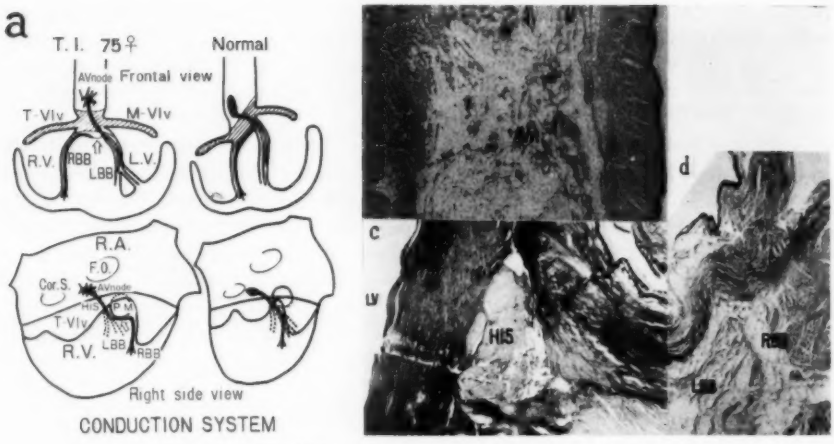


Fig. 4. a. Schema. M-Vlv.: mitral valve, T-Vlv.: tricuspid valve, LBB: Left bundle branch, RBB: right bundle branch, Cor. S.: coronary sinus, F. O.: foramen ovale, P. M.: pars membranacea.
b. A-V node (AVn). Widely scattered nodal cells. 20X Weigert van Gieson stain.
c. His bundle (HIS). Median position of His bundle. 20X Weigert van Gieson stain.
d. Right and left bundle branches (RBB and LBB).

The other findings included multiple old and fresh foci of cerebral softenings and acute confluent bronchopneumonia.

Discussion

Levocardia with total or partial inversion of abdominal viscera is a rare anomaly, which is usually associated with major congenital cardiac malformations and sometimes with splenic anomaly. The low incidence of this anomaly was pointed out by Campbell[6] as only 14 cases found between 1947 and 1955 and by Monma[7] as 8 cases found between 1952 and 1963. Later 8 and 13 cases were reported respectively by Young[8] and Lev.[9] In Japan, the first case reported in 1908 by Miwa[10] was followed by a total of 31 cases by Monma,[7] Kobayashi[11] and others.

Analysis of these 31 cases revealed female preponderence (19 : 9) and short survival not beyond 10 years of age in 87 per cent of the cases (Table I). Keith et al.[2] stated that only 6 per cent of the cases survived beyond 5 years, and the Campbell's oldest case was 19 years of age.[6] The oldest one in the previous reports was a 42-year-old man.[12] Therefore, our case may be the oldest in the world.

Table I. Age and Sex Distribution among the 31 Reported Cases of Isolated Levocardia in Japan

	Male	Female	No description	Total
Premature infant	1	2	1	4
Under 1 yr	5	9		14
1 to 10 yrs	1	5		6
11 to 20 yrs	1	2	1	4
Over 21 yrs	1	1		2
No age given			1	1
Total	9	19	3	31

Table II. Congenital Malformations of the Spleen and Heart in 31 Reported Cases of Isolated Levocardia in Japan

Anomalies of spleen		Anomalies of the heart						
		Total	ASD	VSD	TGV	PS	Miscella-neous	Normal heart
Normal spleen	Normal position	1	1	1		1	1	
	Inversion	4	3	2	3	1		
Abnormal spleen	Asplenia	13	11	10	8	4	3	
	Multiple or accessory spleen	9	6	5	4	2	1	2*
	Multilobulated or bizarre-shaped spleen	4	4	2	3	3		
	Total	31	25	20	18	11	5**	2

ASD: atrial septal defect, VSD: ventricular septal defect, TGV: transposition of the great vessels, PS: pulmonary stenosis.

* (1) 2 Mo. female, Partial inversion of abdominal viscera with multiple spleens.
(2) 42 yrs male, Partial inversion of abdominal viscera with accessory spleen.[12]

** Patent ductus arteriosus, aberrant great vessels and so on.

As to positions of the abdominal viscera in these 31 cases, total inversion was found in 12 cases, and partial inversion in 19. Normal spleen was found in 16 per cent of the cases. Asplenia was seen in 42 per cent, and multiple and/or accessory spleens were in 29 per cent. Only 2 cases (6%) among them had normal heart, one was associated with multiple spleens, and another with an accessory spleen. All of the others had some major cardiac malformations such as atrial septal defect (25 cases, 81%), ventricular septal defect (20 cases, 65%), transposition of the great vessels (18 cases, 58%), and pulmonary stenosis (11 cases, 35%). These associated major cardiac anomalies may explain the short survival of the cases.

As to morphogenesis, D-loop of the cardiac tube coexisting with situs

inversus of the abdominal viscera was supposed to be fundamental for the discordant situs of heart and abdominal viscera.[13] In asplenia and polysplenia syndrome, whole pathologic phenomena could be well explained by an assumption that the formation of the cardiac loop and situs of abdominal viscera were more symmetrical than usual.[5] Besides several symmetrical extracardiac organs, even grossly normal heart in this case showed several symmetrical architectures in detail. Among them, protruded right ventricular shoulder in the frontal view is a common characteristics among other types of congenital heart diseases such as ventricular septal defect and common atrioventricular orifice, which is assumed as an outer reflection of elevated level of the tricuspid ring. These anomalies could be intimately related to incomplete or improper closure of the pars membranacea of interventricular septum.

Outstanding findings in our case consisted of (1) symmetrical 3 lobes of both lungs, (2) symmetrical liver, total inversion of the stomach, duodenum, pancreas and common mesentery, (3) 3 spleens in the inverted position, and (4) symmetrical heart, that is, relatively high position of the tricuspid ring, anomalous pars membranacea of the ventricular septum, anomalous muscle bundle in the left ventricle and symmetrical course of the conduction system. These findings advocate the hypothesis of the symmetry of visceral anlages for morphogenesis of this kind of anomaly.

Acknowledgement

We wish to thank Professor H. Ueda in the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, for his instruction.

This case was presented at the 187th Kanto regional meeting of the Japanese Society of Internal Medicine, on September 9, 1967.

References

1. Nadas, A. S.: Pediatric Cardiology, W. S. Saunders Co., Philadelphia and London, 1963.
2. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart Disease in Infancy and Childhood. MacMillan Co., New York, 1959.
3. Ivemark, B.: Acta pediat. (Suppl.), 104, 1955.
4. Gilbert, E. F., Nishimura, K., and Wedum, B. G.: Circulation **17**: 72, 1958.
5. Moller, J. H., Nakib, A., Anderson, R. C., and Edwards, J. E.: Circulation **36**: 789, 1967.
6. Campbell, M. and Forgacs, P.: Brit. Heart J. **15**: 401, 1953.
7. Monma, K., Tanae, A., Ohshima, M., and Okuni, M.: Jap. Heart J. **5**: 243, 1964.
8. Young, M. D. and Griswold, H. E.: Circulation **3**: 202, 1951.
9. Lev, M. and Rowlatt, U. F.: Am. J. Cardiol. **8**: 216, 1961.
10. Miwa, S. and Utsuno, K.: Zikazasshi **101**: 1, 1908 (in Japanese).
11. Kobayashi, Y.: Trans. Soc. Pathol. Japonicae **53**: 66, 1964 (in Japanese).
12. Matsumura, K.: Hokuetsu Igaku Zasshi **43**: 51, 1928 (in Japanese).
13. Van Praagh, R., Van Praagh, S., Vlad, P., and Keith, J. D.: Am. J. Cardiol. **13**: 510, 1964.

AUTHOR INDEX

Agress, C. M. 169, 339
Akasu, M. 241
Aoki, H. 57
Araki, Y. 3
Asano, K. 97, 134, 441
Asano, T. 368

Bette, L. 404
Blümchen, G. 258
Boku, S. 531

Chang, S. Y. 117, 539
Chung, E. K. 504, 593

Ebeling, J. 404
Eguchi, S. 97
Endo, N. 247

Furuse, A. 200, 316, 434, 531

Gondaira, T. 349
Goto, K. 13
Guyton, A. C. 46

Hachiya, T. 247
Hanawa, M. 520
Harumi, K. 295
Hasegawa, T. 200
Hatano, S. 349, 552
Hayase, S. 431
Hiejima, K. 208
Hiraoka, K. 265, 603
Hirasawa, K. 564
Hiroki, T. 64
Hishimoto, Y. 247
Hoshino, K. 134, 441
Hosono, K. 20

Ichinose, S. 247
Iida, Y. 161
Iio, M. 552
Iizuka, T. 411
Inoue, K. 117
Inoue, S. 219
Iriuchijima, J. 487
Ishida, M. 520
Ishii, H. 110
Ito, I. 88, 228, 573
Ito, K. 316, 434, 531
Ito, T. 3, 281
Izuka, K. 453

Kaku, I. 393
Kato, R. 303
Kawai, N. 117, 303
Kawamura, M. 57
Kawanishi, M. 57
Kiefer, H. 258
Kimura, N. 241
Kinouchi, T. 3, 281
Kiriyama, T. 247
Kitamura, K. 473
Kobayashi, Ta. 110
Kobayashi, To. 404
Kogure, T. 57
Koide, T. 228, 349
Koike, S. 552
Kotoda, T. 200
Kumagai, N. 110
Kunieda, T. 20
Kurosawa, T. 3

Lapiccirella, V. 321

Machida, K. 228
Maebashi, M. 13
Marumoto, S. 247
Masuda, S. 461
Matsukawa, T. 441
Matsuo, H. 186

Matsuura, T. 247
Miyahara, M. 359
Miyoshi, M. 441
Mizuguchi, T. 34
Mizuno, A. 200, 316, 434
Mori, M. 552
Morii, T. 219, 265, 509
Morinari, H. 552
Morooka, S. 573
Murakami, M. 461
Murao, M. 552
Murata, K. 453

Nagai, T. 461
Nagano, M. 57
Nagasaka, M. 3, 281
Nagatani, M. 420
Naito, C. 180
Nakajo, T. 520
Nakamura, Ha. 564
Nakamura, Hi. 142, 539
Nakamura, K. 3, 281
Nakanishi, A. 219, 228, 265, 411
Nakazawa, K. 453
Niki, I. 247
Nishide, K. 473
Nishimura, H. 494
Nohara, F. 316
Nohara, T. 564

Ochiai, M. 247
Ohkawa, S. 411
Ohno, K. 88
Ohya, N. 473, 564
Okada, R. 219, 265, 411, 509, 603
Okubo, K. 453
Oreshkov, V. I. 332
Oshima, Y. 453
Ozeki, K. 228

Reindell, H. 258

Sagawa, K. 46
Saigusa, M. 200, 316, 434, 520, 531
Saito, Y. 88, 573
Sakai, S. 473, 564
Sakamoto, T. 117, 142, 303, 420, 539
Sakamoto, Ya. 208
Sakamoto, Yo. 303
Sakashita, I. 441
Sano, T. 64, 161
Sasamoto, H. 20
Sato, F. 200
Sato, S. 161
Sato, T. 13
Sawaguchi, S. 520
Sawanobori, T. 64
Sawayama, T. 247
Seki, K. 3
Sekimoto, H. 461
Shiina, S. 208
Shikata, T. 247
Shimada, H. 219, 265, 411, 509
Shimazaki, S. 247
Shinoda, A. 564
Shiozaki, K. 97
Sokabe, H. 494
Sugimoto, T. 46
Sugishita, Y. 228
Sugiura, M. 228, 265, 411, 509, 573, 603
Suzuki, F. 64, 161

Tagawa, H. 142
Takabatake, Y. 228
Takada, A. 473
Takahashi, M. 3, 281
Takeda, T. 88, 142
Takeuchi, J. 473, 564
Tanabe, T. 225
Tanaka, M. 97
Tomizaka, S. 57
Trethewie, E. R. 583
Tsuchida, Y. 520
Tsuchiya, S. 208
Tsuzuki, M. 258

Uchida, Y. 228, 517
Ueda, H. 1, 88, 117, 142, 186, 228, 295, 303, 349, 420, 517, 539, 552, 573
Ueda, K. 228, 295
Ueda, T. 359
Ueno, A. 88
Uozumi, Z. 117, 142, 303, 420, 539
Ushi, M. 180
Utsu, F. 241

Wada, J. 105
Washio, M. 97, 134
Wegner, S. 169, 339

Yamada, T. 117, 142, 539
Yamaguchi, H. 573
Yamanaka, Y. 180
Yasuda, H. 186, 228
Yasuda, Y. 461
Yasumura, A. 461
Yomoda, M. 241
Yoshinaga, K. 13
Yoshitoshi, Y, 3, 180, 281

SUBJECT INDEX

A

ABC electrocardiographic diagnosis, of ventricular septal defect, 583
Abdominal murmurs,
in renovascular hypertension, 142
phonocardiographic and arteriographic evaluation of, 142
Abnormal distribution of pulmonary blood flow, hemodynamics of, 20
in patients with cardiac disorders, 20
Abnormal muscle bundle in the left ventricle, in isolated levocardia, 603
Absence of inferior vena cava, 200
Acetylcholine-induced-fibrillation, 162
Acid and alkali treatment, renin-angiotensinogen reaction, 494
Acid mucopolysaccharides, 453
Aconitine-induced-fibrillation, 162
Acquired cardiopathies, biplane cinefluorography in, 404
Acquired pulmonary regurgitation, 420
Aldosterone, effects on renal sodium and potassium excretion, 3
Aldosteronism, primary or secondary, 13
α-Lipoprotein, 184
Alveolar cell, type I and II, 441
Ammonia, effect on myocardial metabolism, 368
Amylnitrite, 142
Analog computer, in the study on spatial velocity electrocardiogram, 64
Analog computer simulation, 281
Aneurysm, in aortitis syndrome, 77
Aneurysm formation, in aortitis syndrome, 88
Angina pectoris, treatment of, 359
Anginin, clinical evaluation of the effect on ischemic heart diseases, 359
Angiocardiography, in Fallot's tetralogy, 531
Angiography, in hyperthyroidism, 247
Angiotensin, and catecholamine, interrelationship between, 13
Angiotensinases,
inhibition of, 494
in plasma and kidney, 494
Anitschkow myocyte, in myocardial tissue, 578
Anomalous systemic venous connection, coronary sinus rhythm in, 200
Anti-aorta antibody, 573
Anti-arrhythmic agents,
new, 161
mode of action of, 161
Anti-bradykinin preparation, 359
Antiserum, against microsome fractions of renal cortex, 461
Anti-streptodornase, 110
Anti-streptokinase, 110
Antistreptolysin O, 110
Anxiety state, 321
Aorta, hypoplasia of, 434
Aortic arteriosclerosis, 461
Aortic constriction, left ventricular hypertrophy and heart failure induced by, 393
Aortic diastolic regurgitant murmur, point of maximum intensity of, 117
Aortic insufficiency, etiology of, 120
Aortic regurgitation, in aortitis syndrome, 77, 88
Aortic stenosis, surgical treatment of congenital valvular and subvalvular, 97
Aortic wall,
study on lipids and fatty acids on, 34
uptake of C^{14}-cholesterol, 180
Aortitis syndrome (Takayasu's arteritis), 118, 143, 539, 573
clinical and pathological studies of, 76
with aneurysm formation, 88
Apex cardiogram, 332
Arterial oxygen saturation, in Fallot's tetralogy, 531
Arterial pressure, systemic, and local peripheral resistance, 487
Arteriography, in aortitis syndrome, 80
Arteriole,
coronary vascular lesion, 473
in experimental hypertension, 473
in hypercholesterolemia, 473
Arteriovenous anastomoses, in thyroid gland, 247
Arteritis, experimental, in rabbits, 573
Artery, small,
coronary vascular lesion, 473
in experimental hypertension, 473
in hypercholesterolemia, 473

Asynchronism of cardiac contraction, cineangiographic observation during ventricular pacing, 295
Atherogenesis, 184
Atheroma, 461
Atherosclerosis,
study on lipids and fatty acids in, 34
experimental, 34
Atrial pacing, 295
Atrial septal defect, 134
Atrioventricular dissociation, reappraisal of, 593
Atrioventricular nodal rhythm, digitalis-induced, 504
Atypical coarctation of the aorta, in aortitis syndrome, 88
Auscultation, 142
of aortic diastolic murmur, 118
of arterial stenotic lesion, 539
of thyroid murmur, 247
Austin Flint murmur, right-sided, 303
Automatic development machine, 404
A-V nodal rhythm, 504

B

β-Lipoprotein, 184
Biplane cinefluorography,
importance of, 404
in congenital and acquired cardiopathies, 404
Bipolar electrode, for the study of renal nerve activity, 564
Biventricular hypertrophy, and ABC lead tracings, 583, 590
Blood pressure,
elevation pattern of, 187
in experimental hypertension, 473
propranolol in patient with Fallot's tetralogy, 531
Body fluid, compartmental model of, 281
Bradykinin, preparations of anti-, 359
Bronchial compression, in quadrivalvular heart disease, 303

C

C^{14}-acetate, 368
-alanine, 368
-cholesterol, uptake of, 180
-glutamic acid, 368
-glutamine, 368
-glycine, 368
Calcium-induced-fibrillation, 162
Carbon dioxide, and regional cerebral blood flow, 349
Cardiac contraction,
asynchronism of, 295
cineangiocardiographic observation of, 295
Cardiac cycle, phasic analysis of, 332
Cardiac hypertrophy,
experimentally induced, 393
myocardial nucleic acids and proteins metabolism, 393
Cardiac movement,
in biplane cinefluorography, 404
Cardiac output,
indirect, 339
systemic arterial pressure, 487
Cardiac phases, 169
determination of stroke volume, 339
Cardiac rupture, 416
clinicopathological study on, 265
following myocardial infarction, 265
in the aged, 265
Cardiac surgery, parenteral fluid therapy in childhood, 520
Carotid tracing, phasic analysis of cardiac cycle, 332
Cast preparation, of thyroid gland, 247
Catecholamines, interrelationship between angiotensin and, 13
Cerebral blood flow, regional, external measurement in man, 349
Cerebral hemorrhage,
administration of vascular permeability factor, 461
microscopic, 186
multiple punctate, 186
single massive, 186
Cerebral softening, 186
Cerebrospinal fluid, drainage of, 316
Cerebrovascular diseases, regional cerebral blood flow in, 349
Cerebrovascular lesions, in experimental renal hypertensive rats, 186
Cholesterol, 453
C^{14}-, 180
esters, fatty acids composition of, 34
Chondroitin sulfate,
A, B and C, 453
in atherosclerotic patients, 453
Chronic cardiopulmonary disorders, pulmonary regional ventilation, perfusion relationships in, 552
Chronic panaortitis, 88
Cineangiocardiographic observation,
during ventricular pacing, 295
on the asynchronism of cardiac contraction, 295

Circumferential shortening rate, 228
Clearance curve, K^{85}, measurement of regional cerebral blood flow, 349
Clinicopathological study, on the cardiac rupture, 265
Closing process of ventricular septal defect, 219
Coarctation of the aorta, and ABC lead tracings, 77, 583, 586
Compartmental model of body fluid, 281
Complemental fixation test, in aortitis syndrome, 573
Conduction system, in isolated levocardia, 603
Congenital cardiopathies, biplane cinefluorography in, 404
Congenital heart disease, and isolated levocardia, 603
Congenital septal defect, 208
Continuous murmur,
in Lutembacher syndrome, 134
significance of, 134
Contractile protein, 393
Coronary arteriogram and ECG change, 258
Coronary arteriography,
clinical experience of, 258
Paulin's method, 258
Coronary artery,
partial hypoplasia of the left ventricle, 509
single, 509
Coronary disease, 321
Coronary heart disease, 265, 411
Coronary sinus rhythm, 200
Coronary vascular lesion,
in experimental hypertension, 473
in hypercholesterolemia, 473
Cotton seed oil, hypercholesterolemia, 473

D

Diaphragmatic breathing, altered, 321
Digitalis, 225
effect of, on myocardial metabolism, 368
-induced arrhythmia, 504
-induced double atrioventricular nodal rhythm, 504
Dilatation of the aorta, in aortitis syndrome, 88
Diphenylhydantoin, 161
Distribution index, of pulmonary blood flow, 20
DNA in cardiac failure, 393
Dye dilution curve, in Fallot's tetralogy, 531

E

ECG change and coronary arteriogram, 258
Ejection period, phasic analysis of cardiac cycle, 332
Ejection times, determination of stroke volume, 339
Elastic lamina, internal, 473
Electrical alternans, digitalis-induced arrhythmia, 504
Electrocardiograms, in Marfan's syndrome, 210
Electron microscopic study, of pulmonary alveolar lesions, 441
Elevation pattern of blood pressure, 187
End-diastolic volume and pressure, 228
Endomyocardial fibrosis, 1
Enzyme,
in myocardium in experimental hypertension, 57
inhibitors on the angiotensinase activity, 494
Eosinophilic body, in myocardial tissue, 578
Erythrocytes, formalin preserved,
hemagglutination of, 110
treated with tannic acid, 110
Etiology of aortic insufficiency, 120
Excitation, spread of, 295
Experimental arteritis, produced immunologically in rabbits, 573
Experimental hypertension,
arteriole in, 473
coronary vascular lesion in, 473
enzyme activity in the myocardium in, 57
small artery in, 473
Extracorporeal circulation,
fluid therapy following cardiac surgery, 520

F

Fallot's tetralogy,
and ABC lead tracings, 583
hemodynamic effects of propranolol in, 531
Fatty acids,
composition of, in the study on lipids, 34
of the plasma and aortic walls, 34
Fibrillation,
aconitine-induced, 162
acetylcholine-induced, 162
calcium-induced, 162
Fibrinoid necrosis, 186
First derivative electrocardiogram, for myocardial infarction, 75
Filtration theory, 180
Flow,
external measurement of regional cerebral, 349
local, 487
superior mesenteric, 487
Fluid therapy,
after cardiac surgery in childhood, 520

maintenance dose, 520
Force-velocity relationship, 228
Frontal P wave axis, 201
Functional phonocardiography, 142

G

Galactosamine, 453
Gas exchange, 552
Gel-filtration, 462
Geriatric heart, 265
Geriatrics, 219
Gerontology, 603
Glomerulonephritis, streptococcus, 110
Glucosamine, 453
Glycolysis, in cardiac metabolism, 57
Goldblatt operation, in experimental hypertension, 473

H

Heart disease, ischemic, effect of pyridinolcarbamate (Anginin) on, 359
Heart disease, quadrivalvular, 303
Heart failure,
experimentally induced, 393
myocardial nucleic acids and proteins metabolism, 393
Heart metabolism, in experimental hypertension, 57
Heart rate, effect of propranolol in patient with Fallot's tetralogy, 531
Heart sound, second,
in arterial stenotic lesion, 539
reversed splitting of, 539
Heart surgery, pulmonary alveolar lesions following, 441
Heart valve substitute, 105
Hemagglutination,
-inhibition reaction, 461
of formalin preserved erythrocytes, 110
Hemodilution, fluid therapy following cardiac surgery, 520
Hemodynamic studies, of mitral valve disease, 241
Hexosamine,
effects of chondroitin sulfate on, 453
in atherosclerotic patients, 453
Hypercholesterolemia, in coronary vascular lesion, 473
Hypertension,
coronary vascular lesion in experimental, 473
in interrelationship between angiotensin and catecholamines, 13
pulmonary, in ventricular septal defect, 434
regional cerebral blood flow in, 349
renal, 180
renovascular, 539
reversed splitting of the second heart sound, 539
short-term, 180
Hypertensive rats, experimental, renal, 186
Hyperthyroidism,
severity of, 247
thyroid murmur, 247
Hypertonic saline, constant infusion of, 281
Hypertrophic subaortic stenosis, surgical treatment of, 97
Hypoplasia, of left ventricle,
with rudimentary right coronary artery, 509
with partially fused kidney, 509
Hypoplastic left heart syndrome, 509
Hypoxia, 552

I

Idiopathic cardiomegaly, and endomyocardial fibrosis, 1, 228
Idiopathic hypertrophic subaortic stenosis, 228
Image intensifier, for biplane cinefluorography, 404
Immunofluorescent technique, 461
Impulse generator, 404
Inclusion body, in pulmonary alveolar cell, 441
Incorporation ratio, of glycine-2-C^{14} into nucleic acids and proteins, 393
Inferior vena cava, absence of, 200
Inhibition of angiotensinase in plasma and kidney in the rat, 494
Injuries, effect on the arterial wall, 183
Inotropic effect, 228
Interaction between digitalis and other drugs, 225
Intermediary metabolism of myocardium, 359
Internal elastic lamina, 473
Intracardiac phonocardiography, in acquired pulmonary artery stenosis, 420
Intramural arteriosclerosis,
in coranary artery vascular lesion, 473
in experimental hypertension, 473
in hypercholesterolemia, 473
Inverted distribution, of pulmonary arterial flow, 27
Ischemic electrocardiographic change, and alterations in cardiac function, 46
Ischemic heart disease, the effect of pyridinolcarbamate (Anginin) on, 359
Isoproterenol, 142
in patients with idiopathic cardiomegaly, 228

in patients with valvular diseases, 228
left ventricular performance during the infusion of, 228
Isovolumetric contraction time, left ventricular, 169, 332

J

Jone's criteria, 110

K

Kalium excretion,
during mannitol diuresis, 3
renal, 3
Kidney,
inhibition of angiotensinase, 494
partially fused, and partial hypoplasia of the left ventricle, 509
Kidney cortex, vascular permeability factor in, 461
Krypton-85 saline solution, and external measurement of regional cerebral blood flow, 349

L

Lanolin, 473
Left atrial pressure,
and distribution of pulmonary blood flow, 20
in mitral stenosis, 241
Left atrial pressure pulse, 241
Left atrial rhythm, 201
Left axis deviation,
hypoplasia of the left ventricle, 509
specific combination of conduction disturbance with, 411
Left bundle branch block, spatial velocity electrocardiogram in, 64
Left heart failure, distribution of pulmonary blood flow in, 27
Left ventricular end-diastolic volume and pressure, 228
Left ventricular hypertrophy,
and ABC lead tracings, 583
spacial velocity electrocardiogram in, 64
Left ventricular isovolumetric contraction time, determinants of, 169
Left ventricular performance, in isoproterenol infusion, 228
Left ventricular pressure, quantitative effect of low coronary pressure on, 46
Levocardia,
isolated, with polysplenia, 603
special reference to minor cardiac abnormalities, 603
Lipids, of the plasma and aortic walls, 34
Local flow, 487
Low coronary pressure, quantitative effect of, on left ventricular pressure, 46
Lutembacher syndrome, continuous murmur in, 134

M

Mannitol diuresis, 3
Marfan's syndrome,
associated with subacute bacterial endocarditis and the WPW syndrome, 208
Masugi-nephritis, hypertension caused by, 57
Maximum cardiac pressure, 46
Mechanical systole, 332
Mechanocardiography, in quadrivalvular heart disease, 303
Media/diameter ratio, in coronary vascular lesion, 473
Media plaque, fatty acid composition of, 34
Mediastinal teratoma, cause of acquired pulmonary artery stenosis, 420
Metabolism, myocardial, of protein and amino acids, 368
Metabolism of myocardium, intermediary, 368
Methoxamine, 142
Microelectrode, 162
Microscopic cerebral hemorrhage, 187
Microsomal protein, 393
Microsome fractions of renal cortex, antiserum of, 461
Mitral insufficiency, 241
Mitral stenosis, left atrial pressure in, 134, 241
Mitral valve disease, hemodynamic studies of, 241
m-RNA, metabolism in cardiac hypertrophy and heart failure, 393
Multiple punctate cerebral hemorrhage, 186
Myocardial fibrosis, 265
Myocardial incompetence, reversed splitting of the second sound, 539
Myocardial infarction,
cardiac rupture following, 265
septal perforation following, 411
spatial velocity electrocardiogram in, 64
Myocardial metabolism, of protein and amino acids, 368
Myocardial nucleic acids, and proteins metabolism in experimentally induced cardiac hypertrophy and heart failure, 393
Myocardium,
coronary vascular lesion, 473
enzyme activity in, 57
in experimental hypertension, 57

intermediary metabolism of, 368

N

Natrium,
homeostasis of, 281
reabsorption, threshold theory of, 281
regulatory system of, 281
Natrium excretion,
during mannitol diuresis, 3
renal, 3
Neurocirculatory asthenia, pathogenesis of, 431
Nonspecific aortitis, 88

O

Oxidative metabolism, in cardiac metabolism, 57
Oxygen, 100%, and regional cerebral blood flow, 349

P

P wave axis, frontal, 201
Patent ductus, and ABC lead tracings, 583
Patent ductus arteriosus, calcified, 316
Paulin's method,
clinical experience, 258
coronary arteriography, 258
Pentose monophosphate shunt,
in cardiac shunt, 57
Peripheral resistance,
local, on systemic arterial pressure, 487
Persistent left superior vena cava, 200
Phonocardiography,
in arterial stenotic lesion, 539
in Marfan's syndrome, 213
in renovascular hypertension, 142
of aortic diastolic regurgitant murmur, 118
phasic analysis of cardiac cycle, 332
quadrivalvular heart disease, 303
thyroid murmur, 247
Phospholipid, fatty acids composition of, 34
Physical diagnosis, 142
Plasma, inhibition of angiotensinase in the rat, 494
Plasma intima, fatty acid composition of, 34
Plasmatic inhibition, 186
Polygraphic tracing, phasic analysis of cardiac cycle, 332
Polysplenia, isolated levocardia with, 603
Potassium excretion,
during mannitol diuresis, 3
renal, 3
Pressure elevation time, phasic analysis of cardiac cycle, 332
Primary or secondary aldosteronism, in interrelationship between angiotensin and catecholamine, 13
Propranolol, hemodynamic effects, in patients with Fallot's tetralogy, 531
Proteins metabolism, in experimentally induced cardiac hypertrophy and heart failure, 393
Protodiastole, 332
Pulmogram, MAA-, 20
Pulmonary alveolar lesions, following open heart surgery, 441
Pulmonary artery stenosis,
acquired, 420
caused by mediastinal tumor, 420
Pulmonary blood flow,
abnormal distribution of, 20
in patients with cardiac disorders, 20
Pulmonary edema, after cardiac surgery, 526
Pulmonary hypertension, in ventricular hypertension, 434
Pulmonary regional ventilation-perfusion relationships,
hypoxia, 552
in chronic cardiopulmonary disorders, 552
influence of body position, 552
inhalation scintiscanning, 552
perfusion scintiscanning, 552
Pulmonary regurgitation, 303
acquired, 420
Pulmonary stenosis, and ABC lead tracings, 583
Pulmonary surfactant, 441
Pulsed radiation, 404
Pulseless disease, 77, 88
Pyridinolcarbamate, clinical evaluation of the effect on ischemic heart diseases, 359

Q

QT prolongation, and reversed splitting of the second heart sound, 539
Quadrivalvular heart disease, 303
Quanta noise, 405

R

Rabbit,
coronary vascular lesion, 473
experimental hypertension in, 473
hypercholesterolemia, 473
Regurgitant murmur,
aortic, diastolic, 117
Renal artery stenosis, 142
Renal cortex, antiserum against microsome fraction of, 461
Renal hypertension, 180

cardiac metabolism in, 57
Renal ischemia, 461
Renal nerve activity, in left stellate ganglion stimulation, 564
Renal nerves, afferent impulses in, 517
Renal sodium and potassium excretion,
during mannitol diuresis, 3
effects of aldosterone and spirolactone on, 3
Renal tubular function, nervous control of, 564
Renin-angiotensinogen reaction, 494
Renovascular hypertension,
evaluation of abdominal murmur in, 134
in aortitis syndrome, 77, 88, 539
Rheumatic fever, 110
Rheumatic heart disease, 110
Right bundle branch block,
and left axis deviation, specific combination of conduction disturbance with, 411
spatial velocity electrocardiogram in, 64
Right-sided aortic diastolic murmur, 117
Right ventricular hypertrophy,
and ABC lead tracings, 583
spatial electrocardiogram in, 64
Right ventricular pressure, 531
Roentgenography, and PMI of aortic diastolic murmur, 118

S

Saline, hypertonic,
constant infusion of, in the dog, 281
kinetic analysis, 281
Scarlet fever, 110
Scintiscanning,
inhalation, 552
pulmonary perfusion, 552
Second heart sound,
arterial stenotic lesions in, 539
reversed splitting of, 539
Semiselective coronary arteriography, 258
Septal perforation, 265
following acute myocardial infarction, 411
with special reference to types of infarction and a study of conduction system, 411
Serum lipids, effects of chondroitin sulfates in atherosclerotic patients, 453
Single coronary artery, 509
Single massive cerebral hemorrhage, 186
Situs inversus, isolated levocardia with, 603
Sodium, excretion, renal, and during mannitol, diuresis, 3
homeostasis, 281
reabsorption, thereshold theory of, 281
reabsorption in stellate ganglion stimulation diuresis, 564
transport in stellate ganglion stimulation diuresis, 564
Spacial velocity electrocardiogram, 64
Spirolactone, effects on renal sodium and potassium excretion, 3
Splenic contraction, 487
S-RNA, metabolism in cardiac failure, 395
Stellate ganglion stimulation diuresis, 564
Stenosis of pulmonary artery, 420
Steroid hormone, in aortitis syndrome, 76
Streptococcal infection, 110
Streptococcus glomerulonephritis, 110
Streptococcus viridans, 210
Streptokinase-streptodornase, erythrocytes sensitized with, 110
Stroke volume, determination of,
ejection times from, 339
from left ventricular isovolumetric contraction, 339
Subacute bacterial endocarditis, 208, 219
Subaortic stenosis, idiopathic hypertrophic, 228
Subvalvular aortic stenosis, surgical treatment of, 97
Superior mesenteric flow, 487
Superior vena cava, persistent, 200
Symmetrical heart, in isolated levocardia, 603
Sympathetic nervous system, inhibitory mechanism of, to protect against hypertensive state, 11
Systemic pressure, and local peripheral resistance, 487
Systole, mechanical, 332
Systolic bulge, of the ventricle, 295

T

Takayasu's arteritis, 573
Takayasu's disease, 77
Tannic acid, 110
Television camera, 404
Tetrodotoxin, 161
Threshold theory, of Na reabsorption, 281
Thrombosis, 453
Thrombus formation time, 453
Thyroid murmur, origin and clinical significance, 247
Total peripheral resistance, in Fallot's tetralogy, 531
Transistor control, in biplane cinefluorography, 404
Treatment, of angina pectoris, 359
Triglyceride, fatty acids composition of, 34
Tyramine, blood pressure response to, before

and after angiotensin infusion, 17

U

U/L ratio, of pulmonary arterial blood flow, 20
Ultrasonic nebulizer, 552
Uptake of C^{14}-cholesterol,
by the aortic wall, 180
effect of "short-term" hypertension on, 180
Urinary K/Na ratio, 3

V

Valvular heart disease, 228
Valvular stenosis, surgical treatment of, 97
Varidase, erythrocytes sensitized with, 110
Vascular lesion, vascular permeability factor, 461
Vascular permeability factor from the kidney cortex, 461
Vectorcardiogram by Frank's lead system, 65
Ventilation-perfusion relationships, 552
Ventricle, systolic bulge of, 295
Ventricular contraction, initial phase of, 332
Ventricular dp/dt, right, 531
Ventricular filling, rapid, slow and active, 332
Ventricular isovolumetric contraction, left, and determination of stroke volume, 339
Ventricular output curve, studied with coronary arterial pressure, 46
Ventricular pacing, cineangiographic observation on the asynchronism of cardiac contraction, 295
Ventricular premature beats, spatial velocity electrocardiogram in, 64
Ventricular pressure, right, 531
Ventricular rupture, 265
Ventricular septal defect,
ABC electrocardiographic diagnosis of, 583
and subacute bacterial endocarditis, 219
angiography of, 434
in the aged, 219
its closing process, 219
sizes of the great arteries, 434
surgical significance of preoperative assessment, 434
Vicious cycle of cardiac deterioration, 46

W

Water electrolyte balance study, and cardiac surgery in childhood, 520
Water loss, in cardiac surgery in childhood, 520
WHO classification, of ischemic heart diseases, 359
Wolff-Parkinson-White syndrome, 208

KANAMYCIN

KANAMYCIN was discovered by Dr. Hamao Umezawa and developed by the world famous laboratories of Meiji Seika Kaisha, Ltd. KANAMYCIN is medicine's answer to a wide variety of diseases caused by gram-positive, gram-negative and acid-fast bacteria. Pathogens resistant to most antibiotics are successfully destroyed by KANAMYCIN. Dramatic results have been obtained in treating tuberculosis.

INDICATIONS

1. Respiratory tract infections due to Staphylococcus, Pneumococcus, Streptococcus viridans and Hemophilus influenzae.
2. Urinary tract infections due to Staphylococcus, Escherichia coli, Pseudomonas aeruginosa and Proteus vulgaris.
3. Gonococcal infections.
4. Suppurative infections due to Staphylococcus, Pneumococcus and Pseudomonas aeruginosa.
5. Bacillary dysentery.
6. Acute diarrhea.
7. Adnexitis.
8. Pulmonary tuberculosis, urinary tuberculosis, genital tuberculosis, and tuberculosis of the lymphnode.
9. Prophylactic use for post-operative infections.
10. Weil's disease.

CONTENTS

PAGE

Editorial: Afferent Impulses in the Renal Nerves. *Hideo Ueda and Yasumi Uchida* 517

Parenteral Fluid Therapy Following Cardiac Surgery in Childhood. *Yoshiaki Tsuchida, Toshio Nakajo, Masao Hanawa, Shigenori Sawaguchi, Masanobu Ishida, and Masahiro Saigusa* 520

Hemodynamic Effects of Propranolol in Patients with Fallot's Tetralogy at Rest. *Kenji Ito, Akira Furuse, Sohgen Boku, and Masahiro Saigusa* 531

Reversed Splitting of the Second Heart Sound in Arterial Stenotic Lesions. *Tsuguya Sakamoto, Tetsuro Yamada, Zen'ichiro Uozumi, Sheng Yu Chang, Hidezo Nakamura, and Hideo Ueda* 539

Pulmonary Regional Ventilation-Perfusion Relationships in Chronic Cardiopulmonary Disorders. II. Scintiscanning Method. *Hideo Ueda, Hajime Morinari, Shuichi Hatano, Masahiro Iio, Masashi Mori, Shigeo Koike, and Makoto Murao* 552

Nervous Control of the Renal Tubular Function. *Jugoro Takeuchi, Nobuo Ohya, Shuichiro Sakai, Haruo Nakamura, Tetsuo Nohara, Kunihiko Hirasawa, and Akira Shinoda* 564

Experimental Arteritis Produced Immunologicâlly in Rabbits. *Hideo Ueda, Yoshimi Saito, Shigenori Morooka, Iwao Ito, Hisomu Yamaguchi, and Masaya Sugiura* 573

ABC Electrocardiographic Diagnosis of Ventricular Septal Defect. *E. R. Trethewie* 583

Special Article:

A Reappraisal of Atrioventricular Dissociation. *Edward K. Chung* 593

Case Report:

Isolated Levocardia with Polysplenia in an Aged with Special Reference to Minor Cardiac Abnormalities. *Masaya Sugiura, Ryozo Okada, and Keisuke Hiraoka* 603

Author Index 609

Subject Index 612

Subscription rate: U.S. $12.00 post free a year (1 Vol. of 6 Nos.)
Single issue: U.S. $2.50 post free
Orders with remittance should be sent to the following agency:
Nankodo Co., Ltd., 42-6, Hongo 3-chome, Bunkyo-ku, Tokyo, Japan

Supported in part by the Grant in Aid for Publishing Scientific Research Result from the Ministry of Education, Japan.